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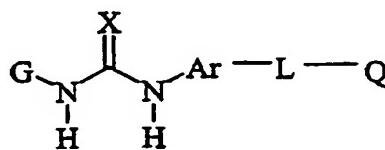
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(54) Title: UREA DERIVATIVES AS ANTI-INFLAMMATORY AGENTS



(I)

(57) Abstract: Disclosed are novel aromatic compounds of formula (I) wherein G, X, Ar, L and Q are defined herein. The compounds are useful in pharmaceutical compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases. Also disclosed are processes of making such compounds. The compounds (I) inhibit cytokine production.

UREA DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

RELATED APPLICATION DATA

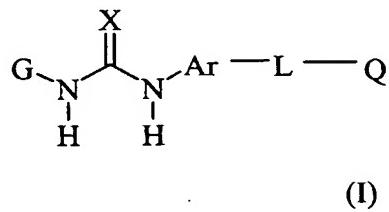
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5 11/16/1999.

TECHNICAL FIELD OF THE INVENTION

This invention relates to novel compounds of formula(I):

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15 wherein G,X,Ar,L and Q of formula(I) are defined below. The compounds of the invention inhibit production of cytokines involved in inflammatory processes and are thus useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease. This invention also relates to processes for preparing these compounds and to pharmaceutical compositions comprising these compounds.

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BACKGROUND OF THE INVENTION

25 Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are important biological entities collectively referred to as proinflammatory cytokines. These, along with several other related molecules, mediate the inflammatory response associated with the immunological recognition of infectious agents. The inflammatory response plays an important role in limiting and controlling pathogenic infections.

Elevated levels of proinflammatory cytokines are also associated with a number of diseases of autoimmunity such as toxic shock syndrome, rheumatoid arthritis, osteoarthritis, diabetes and inflammatory bowel disease (Dinarello, C.A., *et al.*, 1984, *Rev. Infect. Disease* 6:51). In these diseases, chronic elevation of inflammation 5 exacerbates or causes much of the pathophysiology observed. For example, rheumatoid synovial tissue becomes invaded with inflammatory cells that result in destruction to cartilage and bone (Koch, A.E., *et al.*, 1995, *J. Invest. Med.* 43: 28-38). An important and accepted therapeutic approach for potential drug intervention in these diseases is the reduction of proinflammatory cytokines such as TNF (also referred to in its secreted cell-10 free form as TNF α) and IL-1 β . A number of anti-cytokine therapies are currently in clinical trials. Efficacy has been demonstrated with a monoclonal antibody directed against TNF α in a number of autoimmune diseases (Heath, P., "CDP571: An Engineered Human IgG4 Anti-TNF α Antibody" IBC Meeting on Cytokine Antagonists, Philadelphia, PA, April 24-5, 1997). These include the treatment of rheumatoid arthritis, 15 Crohn's disease and ulcerative colitis (Rankin, E.C.C., *et al.*, 1997, *British J. Rheum.* 35: 334-342 and Stack, W.A., *et al.*, 1997, *Lancet* 349: 521-524). The monoclonal antibody is thought to function by binding to both soluble TNF α and to membrane bound TNF.

A soluble TNF α receptor has been engineered that interacts with TNF α . The approach is 20 similar to that described above for the monoclonal antibodies directed against TNF α ; both agents bind to soluble TNF α , thus reducing its concentration. One version of this construct, called Enbrel (Immunex, Seattle, WA) recently demonstrated efficacy in a Phase III clinical trial for the treatment of rheumatoid arthritis (Brower *et al.*, 1997, *Nature Biotechnology* 15: 1240). Another version of the TNF α receptor, Ro 45-2081 25 (Hoffman-LaRoche Inc., Nutley, NJ) has demonstrated efficacy in various animal models of allergic lung inflammation and acute lung injury. Ro 45-2081 is a recombinant chimeric molecule constructed from the soluble 55 kDa human TNF receptor fused to the hinge region of the heavy chain IgG1 gene and expressed in eukaryotic cells (Renzetti, *et al.*, 1997, *Inflamm. Res.* 46: S143).

IL-1 has been implicated as an immunological effector molecule in a large number of disease processes. IL-1 receptor antagonist (IL-1ra) had been examined in human clinical trials. Efficacy has been demonstrated for the treatment of rheumatoid arthritis (Antril, Amgen). In a phase III human clinical trial IL-1ra reduced the mortality rate in patients with septic shock syndrome (Dinarello, 1995, *Nutrition* 11, 492). Osteoarthritis is a slow progressive disease characterized by destruction of the articular cartilage. IL-1 is detected in synovial fluid and in the cartilage matrix of osteoarthritic joints.

Antagonists of IL-1 have been shown to diminish the degradation of cartilage matrix components in a variety of experimental models of arthritis (Chevalier, 1997, *Biomed Pharmacother.* 51, 58). Nitric oxide (NO) is a mediator of cardiovascular homeostasis, neurotransmission and immune function; recently it has been shown to have important effects in the modulation of bone remodeling. Cytokines such as IL-1 and TNF are potent stimulators of NO production. NO is an important regulatory molecule in bone with effects on cells of the osteoblast and osteoclast lineage (Evans, *et al.*, 1996, *J Bone Miner Res.* 11, 300). The promotion of beta-cell destruction leading to insulin dependent diabetes mellitus shows dependence on IL-1. Some of this damage may be mediated through other effectors such as prostaglandins and thromboxanes. IL-1 can effect this process by controlling the level of both cyclooxygenase II and inducible nitric oxide synthetase expression (McDaniel *et al.*, 1996, *Proc Soc Exp Biol Med.* 211, 24).

Inhibitors of cytokine production are expected to block inducible cyclooxygenase (COX-2) expression. COX-2 expression has been shown to be increased by cytokines and it is believed to be the isoform of cyclooxygenase responsible for inflammation (M.K. O'Banion *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1992, 89, 4888.) Accordingly, inhibitors of cytokines such as IL-1 would be expected to exhibit efficacy against those disorders currently treated with COX inhibitors such as the familiar NSAIDs. These disorders include acute and chronic pain as well as symptoms of inflammation and cardiovascular disease.

Elevation of several cytokines have been demonstrated during active inflammatory bowel disease (IBD). A mucosal imbalance of intestinal IL-1 and IL-1ra is present in patients

with IBD. Insufficient production of endogenous IL-1 α may contribute to the pathogenesis of IBD (Cominelli, *et al.*, 1996, *Aliment Pharmacol Ther.* 10, 49). Alzheimer disease is characterized by the presence of beta-amyloid protein deposits, neurofibrillary tangles and cholinergic dysfunction throughout the hippocampal region.

5 The structural and metabolic damage found in Alzheimer disease is possibly due to a sustained elevation of IL-1 (Holden, *et al.*, 1995, *Med Hypotheses*, 45, 559). A role for IL-1 in the pathogenesis of human immunodeficiency virus (HIV) has been identified. IL-1 α showed a clear relationship to acute inflammatory events as well as to the different disease stages in the pathophysiology of HIV infection (Kreuzer, *et al.*, 1997, *Clin Exp Immunol.* 109, 54).

10 IL-1 and TNF are both involved in periodontal disease. The destructive process associated with periodontal disease may be due to a disregulation of both IL-1 and TNF (Howells, 1995, *Oral Dis.* 1, 266).

Proinflammatory cytokines such as TNF α and IL-1 β are also important mediators of septic shock and associated cardiopulmonary dysfunction, acute respiratory distress syndrome (ARDS) and multiple organ failure. TNF α has also been implicated in cachexia and muscle degradation, associated with HIV infection (Lahdiverta *et al.*, 1988, *Amer. J. Med.*, 85, 289). Obesity is associated with an increase incidence of infection, diabetes and cardiovascular disease. Abnormalities in TNF α expression have been noted

15 for each of the above conditions (Loffreda, *et al.*, 1998, *FASEB J.* 12, 57). It has been proposed that elevated levels of TNF α are involved in other eating related disorders such as anorexia and bulimia nervosa. Pathophysiological parallels are drawn between anorexia nervosa and cancer cachexia (Holden, *et al.*, 1996, *Med Hypotheses* 47, 423).

An inhibitor of TNF α production, HU-211, was shown to improve the outcome of closed

20 brain injury in an experimental model (Shohami, *et al.*, 1997, *J Neuroimmunol.* 72, 169). Atherosclerosis is known to have an inflammatory component and cytokines such as IL-1 and TNF have been suggested to promote the disease. In an animal model an IL-1 receptor antagonist was shown to inhibit fatty streak formation (Elhage *et al.*, 1998, *Circulation*, 97, 242).

The abnormal expression of inducible nitric oxide synthetase (iNOS) has been associated with hypertension in the spontaneously hypertensive rat (Chou *et al.*, 1998, *Hypertension*, 31, 643). IL-1 has a role in the expression of iNOS and therefore may also have a role in the pathogenesis of hypertension (Singh *et al.*, 1996, *Amer. J. Hypertension*, 9, 867).

5

IL-1 has also been shown to induce uveitis in rats which could be inhibited with IL-1 blockers. (Xuan *et al.*, 1998, *J. Ocular Pharmacol. and Ther.*, 14, 31). Cytokines including IL-1, TNF and GM-CSF have been shown to stimulate proliferation of acute myelogenous leukemia blasts (Bruserud, 1996, *Leukemia Res.* 20, 65). IL-1 was shown

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to be essential for the development of both irritant and allergic contact dermatitis.

Epicutaneous sensitization can be prevented by the administration of an anti- IL-1 monoclonal antibody before epicutaneous application of an allergen (Muller, *et al.*, 1996, *Am J Contact Dermat.* 7, 177). Data obtained from IL-1 knock out mice indicates the critical involvement in fever for this cytokine (Kluger *et al.*, 1998, *Clin Exp Pharmacol Physiol.* 25, 141). A variety of cytokines including TNF, IL-1, IL-6 and IL-8 initiate the acute-phase reaction which is stereotyped in fever, malaise, myalgia, headaches, cellular hypermetabolism and multiple endocrine and enzyme responses (Beisel, 1995, *Am J Clin Nutr.* 62, 813). The production of these inflammatory cytokines rapidly follows trauma or pathogenic organism invasion.

20

Other proinflammatory cytokines have been correlated with a variety of disease states. IL-8 correlates with influx of neutrophils into sites of inflammation or injury. Blocking antibodies against IL-8 have demonstrated a role for IL-8 in the neutrophil associated tissue injury in acute inflammation (Harada *et al.*, 1996, *Molecular Medicine Today* 2, 482). Therefore, an inhibitor of IL-8 production may be useful in the treatment of diseases mediated predominantly by neutrophils such as stroke and myocardial infarction, alone or following thrombolytic therapy, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, hemodialysis, leukopheresis, granulocyte transfusion associated syndromes, and necrotizing enterocolitis.

Rhinovirus triggers the production of various proinflammatory cytokines, predominantly IL-8, which results in symptomatic illnesses such as acute rhinitis (Winther *et al.*, 1998, *Am J Rhinol.* 12, 17).

- 5 Other diseases that are effected by IL-8 include myocardial ischemia and reperfusion, inflammatory bowel disease and many others.

The proinflammatory cytokine IL-6 has been implicated with the acute phase response. IL-6 is a growth factor in a number in oncological diseases including multiple myeloma
10 and related plasma cell dyscrasias (Treon, *et al.*, 1998, *Current Opinion in Hematology* 5: 42). It has also been shown to be an important mediator of inflammation within the central nervous system. Elevated levels of IL-6 are found in several neurological disorders including AIDS dementia complex, Alzheimer's disease, multiple sclerosis, systemic lupus erythematosus, CNS trauma and viral and bacterial meningitis (Gruol, *et*
15 *al.*, 1997, *Molecular Neurobiology* 15: 307). IL-6 also plays a significant role in osteoporosis. In murine models it has been shown to effect bone resorption and to induce osteoclast activity (Ershler *et al.*, 1997, *Development and Comparative Immunol.* 21: 487). Marked cytokine differences, such as IL-6 levels, exist *in vivo* between osteoclasts of normal bone and bone from patients with Paget's disease (Mills, *et al.*, 1997, *Calcif
20 Tissue Int.* 61, 16). A number of cytokines have been shown to be involved in cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with IL-6 receptor antagonists (Strassmann, *et al.*, 1995, *Cytokines Mol Ther.* 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha as key factors in both symptom formation and in host defense (Hayden, *et al.*,
25 1998, *J Clin Invest.* 101, 643). Overexpression of IL-6 has been implicated in the pathology of a number of diseases including multiple myeloma, rheumatoid arthritis, Castleman's disease, psoriasis and post-menopausal osteoporosis (Simpson, *et al.*, 1997, *Protein Sci.* 6, 929). Compounds that interfered with the production of cytokines including IL-6, and TNF were effective in blocking a passive cutaneous anaphylaxis in
30 mice (Scholz *et al.*, 1998, *J. Med. Chem.*, 41, 1050).

GM-CSF is another proinflammatory cytokine with relevance to a number of therapeutic diseases. It influences not only proliferation and differentiation of stem cells but also regulates several other cells involved in acute and chronic inflammation. Treatment with GM-CSF has been attempted in a number of disease states including burn-wound healing,
5 skin-graft resolution as well as cytostatic and radiotherapy induced mucositis (Masucci, 1996, *Medical Oncology* 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus (HIV) in cells of macrophage lineage with relevance to AIDS therapy (Crowe *et al.*, 1997, *Journal of Leukocyte Biology* 62, 41). Bronchial asthma is characterised by an inflammatory process in lungs. Involved cytokines include
10 GM-CSF amongst others (Lee, 1998, *J R Coll Physicians Lond* 32, 56).

Interferon γ (IFN γ) has been implicated in a number of diseases. It has been associated with increased collagen deposition that is a central histopathological feature of graft-versus-host disease (Parkman, 1998, *Curr Opin Hematol.* 5, 22). Following kidney
15 transplantation, a patient was diagnosed with acute myelogenous leukemia. Retrospective analysis of peripheral blood cytokines revealed elevated levels of GM-CSF and IFN γ . These elevated levels coincided with a rise in peripheral blood white cell count (Burke, *et al.*, 1995, *Leuk Lymphoma*. 19, 173). The development of insulin-dependent diabetes (Type 1) can be correlated with the accumulation in pancreatic islet
20 cells of T-cells producing IFN γ (Ablumunits, *et al.*, 1998, *J Autoimmun.* 11, 73). IFN γ along with TNF, IL-2 and IL-6 lead to the activation of most peripheral T-cells prior to the development of lesions in the central nervous system for diseases such as multiple
25 sclerosis (MS) and AIDS dementia complex (Martino *et al.*, 1998, *Ann Neurol.* 43, 340). Atherosclerotic lesions result in arterial disease that can lead to cardiac and cerebral infarction. Many activated immune cells are present in these lesions, mainly T-cells and
30 macrophages. These cells produce large amounts of proinflammatory cytokines such as TNF, IL-1 and IFN γ . These cytokines are thought to be involved in promoting apoptosis or programmed cell death of the surrounding vascular smooth muscle cells resulting in the atherosclerotic lesions (Geng, 1997, *Heart Vessels Suppl* 12, 76). Allergic subjects produce mRNA specific for IFN γ following challenge with *Vespuila* venom (Bonay, *et al.*, 1997, *Clin Exp Immunol.* 109, 342). The expression of a number of cytokines,

including IFN γ has been shown to increase following a delayed type hypersensitivity reaction thus indicating a role for IFN γ in atopic dermatitis (Szepietowski, *et al.*, 1997, *Br J Dermatol.* 137, 195). Histopathologic and immunohistologic studies were performed in cases of fatal cerebral malaria. Evidence for elevated IFN γ amongst other cytokines was observed indicating a role in this disease (Udomsangpetch *et al.*, 1997, *Am J Trop Med Hyg.* 57, 501). The importance of free radical species in the pathogenesis of various infectious diseases has been established. The nitric oxide synthesis pathway is activated in response to infection with certain viruses via the induction of proinflammatory cytokines such as IFN γ (Akaike, *et al.*, 1998, *Proc Soc Exp Biol Med.* 217, 64).

Patients, chronically infected with hepatitis B virus (HBV) can develop cirrhosis and hepatocellular carcinoma. Viral gene expression and replication in HBV transgenic mice can be suppressed by a post-transcriptional mechanism mediated by IFN γ , TNF and IL-2 (Chisari, *et al.*, 1995, *Springer Semin Immunopathol.* 17, 261). IFN γ can selectively inhibit cytokine induced bone resorption. It appears to do this via the intermediacy of nitric oxide (NO) which is an important regulatory molecule in bone remodeling. NO may be involved as a mediator of bone disease for such diseases as: the rheumatoid arthritis, tumor associated osteolysis and postmenopausal osteoporosis (Evans, *et al.*, 1996, *J Bone Miner Res.* 11, 300). Studies with gene deficient mice have demonstrated that the IL-12 dependent production of IFN γ is critical in the control of early parasitic growth. Although this process is independent of nitric oxide the control of chronic infection does appear to be NO dependent (Alexander *et al.*, 1997, *Philos Trans R Soc Lond B Biol Sci* 352, 1355). NO is an important vasodilator and convincing evidence exists for its role in cardiovascular shock (Kilbourn, *et al.*, 1997, *Dis Mon.* 43, 277). IFN γ is required for progression of chronic intestinal inflammation in such diseases as Crohn's disease and inflammatory bowel disease (IBD) presumably through the intermediacy of CD4+ lymphocytes probably of the TH1 phenotype (Sartor 1996, *Aliment Pharmacol Ther.* 10 Suppl 2, 43). An elevated level of serum IgE is associated with various atopic diseases such as bronchial asthma and atopic dermatitis. The level of IFN γ was negatively correlated with serum IgE suggesting a role for IFN γ in atopic patients (Teramoto *et al.*, 1998, *Clin Exp Allergy* 28, 74).

Compounds which modulate release of one or more of the aforementioned inflammatory cytokines can be useful in treating diseases associated with release of these cytokines. For example, WO 98/52558 discloses heteroaryl urea compounds which are indicated to be useful in treating cytokine mediated diseases. WO 99/23091 discloses another class of 5 urea compounds which are useful as anti-inflammatory agents.

U.S. Pat. No. 5,162,360 discloses N-substituted aryl-N'-heterocyclic substituted urea compounds which are described as being useful for treating hypercholesterolemia and atherosclerosis.

10 The work cited above supports the principle that inhibition of cytokine production will be beneficial in the treatment of various disease states. Some protein therapeutics are in late development or have been approved for use in particular diseases. Protein therapeutics are costly to produce and have bioavailability and stability problems. Therefore a need exists for new small molecule inhibitors of cytokine production with optimized efficacy, 15 pharmacokinetic and safety profiles.

BRIEF SUMMARY OF THE INVENTION

The work cited above supports the principle that inhibition of cytokine production will be 20 beneficial in the treatment of various disease states.

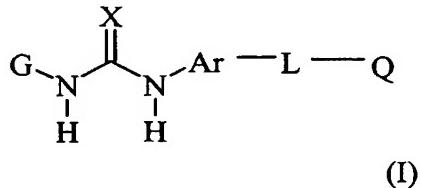
It is therefore an object of the invention to provide novel compounds which inhibit the release of inflammatory cytokines such as interleukin-1 and tumor necrosis factor.

25 It is a further object of the invention to provide methods for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease, using the novel compounds of the invention.

It is yet a further object of the invention to provide processes of preparation of the above- 30 mentioned novel compounds.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the invention there are provided compounds of the formula (I):



10 wherein:

G is:

an aromatic C₆₋₁₀ carbocycle or a nonaromatic C₃₋₁₀ carbocycle saturated or unsaturated;
 a 6-10 membered heteroaryl containing 1 or more heteroatoms chosen from O, N and S;
 or
 15 a 5-8 membered monocyclic heterocycle or a 8-11 membered bicyclic heterocycle, each containing one or more heteroatoms chosen from O, N and S;
 wherein G is substituted by one or more R₁, R₂ or R₃;

Ar is:

20 phenyl, naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, indolenyl, benzothiophenyl, tetrahydroisoquinolinyl, benzimidazolyl, benzofuranyl, indanyl, indenyl or indolyl each optionally substituted by one or more R₄ or R₅ groups;

25

L is a:

C₁₋₁₀ saturated or unsaturated branched or unbranched carbon chain;
 wherein one or more methylene groups are optionally independently replaced by
 30 heteroatoms chosen from O, N and S(O)_m; and
 wherein said L is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optimally substituted by one or more halogen atoms;

Q is:

phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, imidazolyl, benzimidazolyl,
5 furanyl, thienyl, pyranyl, naphthyridinyl, pyrazinyl, pyrazolyl, triazolyl, tetrazolyl,
pyrazolo[3,4-b]pyrimidinyl, purinyl, pyrrolo[2,3-b]pyridinyl, pyrazolo[3,4-b]pyridinyl,
tubercidinyl, oxazo[4,5-b]pyridinyl and imidazo[4,5-b]pyridinyl, which are optionally
substituted with one to three C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, amino, mono- or di-(C₁₋₃
alkyl)amino, mono- or di-(phenyl-C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, phenyl- C₁₋₃-alkoxy
10 or phenylamino wherein the phenyl ring is optionally substituted with one to two
halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl,
morpholino, thiomorpholino, thiomorpholino sulfoxide, thiomorpholino sulfone,
15 piperazinyl, piperidinyl, piperidinonyl, tetrahydropyrimidonyl, cyclohexanone,
cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene
sulfone, tetramethylene sulfide, tetramethylene sulfoxide or tetramethylene sulfone which
are optionally substituted with one to three C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-
(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl or C₁₋₃ alkoxy-C₁₋₃ alkyl;

20 C₁₋₆ alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently
bonded to C₁₋₃ alkyl or C₁₋₅ alkoxyalkyl, phenylamino, wherein the phenyl ring is
optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃
alkyl)amino, C₁₋₆ alkyl-S(O)_m or phenyl-S(O)_m wherein the phenyl ring is optionally
25 substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃
alkyl)amino;

each R₁ is independently:

30 C₃₋₁₀ branched or unbranched alkyl optionally partially or fully halogenated, and
optionally substituted with one to three C₃₋₁₀ cycloalkyl, hydroxy, phenyl, naphthyl ,

pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with 1 to 5 halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, hydroxy, cyano, C₁₋₃ alkoxy which is optionally partially or fully halogenated and NH₂C(O) or mono- or di(C₁₋₃)alkylaminocarbonyl;

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, cyano, hydroxyC₁₋₃alkyl or aryl; or an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

C₃₋₁₀ branched or unbranched alkenyl optionally partially or fully halogenated, and optionally substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned are optionally substituted with 1 to 5 halogen, C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, hydroxy, cyano, C₁₋₃ alkoxy optionally partially or fully halogenated, NH₂C(O) or mono- or di(C₁₋₃)alkylaminocarbonyl; the C₃₋₁₀ branched or unbranched alkenyl is optionally interrupted by one or more O, N or S(O)_m;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three C₁₋₃ alkyl groups;

cyano, halogen;

methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl;
silyl containing three C₁₋₄ independently branched or unbranched alkyl groups optionally partially or fully halogenated;
C₂₋₆ branched or unbranched alkyl-C(O), C₂₋₆ branched or unbranched-S, C₂₋₆ branched
5 or unbranched-S(O), C₂₋₆ branched or unbranched-S(O)₂;

C₂₋₆ alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH and S(O)_m and wherein said alkynyl group is optionally independently substituted with 0-
10 2 or more groups, pyrrolidinyl, pyrrolyl, one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or C₁₋₄ branched or unbranched alkylamino optionally substituted by one or more halogen atoms;

15 each R₂, R₄, and R₅ is independently
a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;

20 C₁₋₆ alkoxy, hydroxy, amino, or mono- or di-(C₁₋₄ alkyl)amino, cyano, halogen;

OR₆;
nitro; or
25 mono- or di-(C₁₋₄ alkyl)amino-S(O)₂ optionally partially or fully halogenated, or H₂NSO₂;

each R₃ is independently:

30 hydrogen, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, thiazolyl,

oxazolyl, triazolyl, tetrazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiophenyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl or indazolyl wherein each of the aforementioned is optionally substituted with one to five phenyl, naphthyl, heterocycle or heteroaryl wherein the heterocyclic and heteroaryl moiety is as hereinabove described in this paragraph, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halogen, hydroxy, oxo, cyano, C₁₋₃ alkoxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy wherein the heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclic or heteroaryl amino wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkylaminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₇-C₁₋₅ alkyl, R₈-C₁₋₅ alkoxy, R₉-C(O)-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkyl(R₁₁)N, carboxy-mono- or di-(C₁₋₅)-alkyl-amino;

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocycle selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopantanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclic ring is optionally independently substituted with 1 to 3 groups selected from phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl,

isoxazolyl, isothiazolyl, C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, halo, cyano, C₁₋₃ alkoxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclicoxy heteroaryloxy wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclicamino or heteroarylarnino wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, an amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₁₂-C₁₋₅ alkyl, R₁₃-C₁₋₅ alkoxy, R₁₄-C(O)-C₁₋₅ alkyl and R₁₅-C₁₋₅ alkyl(R₁₆)N;

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, 20 bicyclohexenyl or bicycloheptenyl each optionally substituted with one to three C₁₋₃ alkyl groups;

C₁₋₄ branched or unbranched alkyl-phenyl-C(O)-C₀₋₄ branched or unbranched alkyl, C₁₋₄ branched or unbranched alkyl-C(O)-C₀₋₄ branched or unbranched alkyl, C₁₋₄ branched or unbranched alkyl-phenyl-S(O)_m-C₀₋₄ branched or unbranched alkyl;

C₁₋₆ branched or unbranched alkyl or C₁₋₆ branched or unbranched alkoxy each is optionally partially or fully halogenated or optionally substituted with R₁₇;

30 C₀₋₆ branched or unbranched alkyl optionally substituted with OR₁₈;

amino or C₁-C₅ branched or unbranched mono- or di-alkylamino optionally substituted with R₁₉;

- Cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

R₂₀C(O)N(R₂₁)-, R₂₂O- or R₂₃R₂₄NC(O)-; R₂₆(CH₂)_mC(O)N(R₂₁)- or R₂₆C(O)(CH₂)_mN(R₂₁)-;

10

C₂₋₆alkenyl substituted by R₂₃R₂₄NC(O)-;

- C₂₋₆ alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, S(O), S(O)₂ or S and wherein said alkynyl group is optionally independently substituted with 0-2 oxo groups, pyrroldinyl, pyrrolyl, one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidine, piperazine, imidazole, phenyl, pyridine, tetrazole, or C₁₋₄ branched or unbranched alkylamino optioanlly substituted by one or more halogen atoms; or

20

aryoyl;

R₆ is a:

- C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with R₂₆;

each R₇, R₈, R₉, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₇, R₁₉, R₂₅ and R₂₆ is independently: nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl or alkylamino mono- or di-C₀₋₄ branched or unbranched optionally partially or fully halogenated;

each R₁₁ and R₁₆ is independently:

hydrogen or C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated;

R₁₈ is independently:

- 5 hydrogen or a C₁₋₄ branched or unbranched alkyl optionally independently substituted with oxo or R₂₅;

R₂₀ is:

- C₁₋₁₀ branched or unbranched alkyl optionally partially or fully halogenated, phenyl or
10 pyridinyl;

R₂₁ is:

hydrogen or C₁₋₃ branched or unbranched alkyl optionally partially or fully halogenated;

- 15 each R₂₂, R₂₃ and R₂₄ is independently:

hydrogen, C₁₋₆ branched or unbranched alkyl optionally substituted by carbonylamino-mono- or di-C₁₋₃alkyl or amino-mono or diC₁₋₃alkyl or wherein said C₁₋₆ alkyl optionally partially or fully halogenated and optionally interrupted by one or more O, N or S, phenyl, pyridine, mono- or di-C₀₋₄ branched or unbranched alkyl optionally partially or
20 fully halogenated and alkylamino;

or R₂₃ and R₂₄ taken together optionally form a heterocyclic or heteroaryl ring;

m = 0, 1 or 2;

25

X = O or S; and

the pharmaceutically acceptable derivatives thereof.

30

In another embodiment of the invention there is provided compounds of the formula(I) as described immediately above, and wherein

G is

- 5 phenyl, naphthyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl,
benzocycloheptanyl, benzocycloheptenyl, indanyl, indenyl, benzofuran-3-one, 4H-
benzo[1,4]oxazine-3-one;
- 10 pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl,
tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl,
benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl,
dihydrobenzothiophenyl, benzoaxazolonyl, benzo[1,4]oxazin-3-onyl, benzodioxolyl,
benzo[1,3]dioxol-2-onyl, tetrahydrobenzopyranyl, indolyl, indolinyl, indolonyl,
15 indolinonyl, phthalimidyl;
- oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl,
morpholinyl, tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene
sulfoxidyl, oxazolinyl, thiazolinyl, imidazolinyl, tetrahydropyridinyl, homopiperidinyl,
pyrrolinyl, tetrahydropyrimidinyl, decahydroquinolinyl, decahydroisoquinolinyl,
20 thiomorpholinyl, thiazolidinyl, dihydrooxazinyl, dihydropyranyl, oxocanyl, heptacanyl,
thioxanyl or dithianyl;

wherein G is substituted by one or more R₁, R₂ or R₃.

25

In another embodiment of the invention there is provided compounds of the formula(I) as described immediately above, and wherein

- 30 G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl,
benzimidazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl,
dihydrobenzofuranyl, dihydrobenzothiophenyl, indanyl, indenyl, indolyl, indolinyl,

indolonyl, indolinonyl, benzofuran-3-one or 4H-benzo[1,4]oxazine-3-one, wherein G is substituted by one or more R₁, R₂ or R₃;

Ar is:

5

naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indanyl, indenyl or indolyl each optionally substituted by one or more R₄ or R₅ groups;

10 L is a:

C₁₋₄ saturated or unsaturated branched or unbranched carbon chain;

wherein one or more methylene groups are optionally independently replaced by heteroatoms chosen from O, N and S(O)_m; and

15 wherein said L is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

Q is:

20 phenyl, naphthyl, pyridinyl or imidazolyl which are optionally substituted with one to three halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, hydroxy, amino, mono- or di-(C₁₋₃ alkyl)amino or mono- or di-(phenyl-C₁₋₃ alkyl)amino;

25 tetrahydropyranyl, tetrahydrofuranyl, morpholino, thiomorpholino, thiomorpholino sulfoxide, piperidinyl, piperidinonyl, tetrahydropyrimidonyl, pentamethylene sulfide, pentamethylene sulfoxide or pentamethylene sulfone which are optionally substituted with one to three C₁₋₃ alkyl, C₁₋₃ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl or C₁₋₃ alkoxy-C₁₋₃ alkyl;

30 each R₁ is independently:

C₃₋₅ branched or unbranched alkyl optionally partially or fully halogenated, and
optionally substituted with one to three C₃₋₆ cycloalkyl, hydroxy, phenyl, thienyl, furyl,
isoxazolyl or isothiazolyl; each of the aforesaid being optionally substituted with 1
to 5 halogen, C₁₋₃ alkyl which is optionally partially or fully halogenated, hydroxy, cyano
5 or C₁₋₃ alkoxy optionally partially or fully halogenated;

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl
optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃
alkyl groups optionally partially or fully halogenated, CYANO, hydroxyC₁₋₃alkyl or
10 phenyl; or an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl,
bicyclopentanyl or bicyclohexanyl wherein one to three ring methylene groups are
independently replaced by O, S, CHO, >C=O, >C=S or NH; or
15 silyl containing three C₁₋₄ independently branched or unbranched alkyl groups optionally
partially or fully halogenated;

each R₃ is independently:

hydrogen, phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrrolylidinyl, imidazolyl
20 or pyrazolyl, wherein each of the aforesaid is optionally substituted with one to
five phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this
paragraph, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully
halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl,
bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl,
25 halogen, oxo, hydroxy, cyano, C₁₋₃ alkoxy optionally partially or fully halogenated,
phenyloxy, naphthoxy, heteraryloxy or heteroclicoxy wherein the heteraryl or
heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or
di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclic or heteroaryl amino
wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this
30 paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄
alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋

3) alkylamino-S(O)₂, R₇-C₁₋₅ alkyl, R₈-C₁₋₅ alkoxy, R₉-C(O)-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkyl(R₁₁)N or carboxy-mono- or di-(C₁₋₅)-alkyl-amino;

5 C₁₋₃ alkyl or C₁₋₃ alkoxy optionally partially or fully halogenated or optionally substituted with R₁₇;

Cyclopropyloxy, cyclopentyloxy or cyclohexyloxy which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

10 C₀₋₆ branched or unbranched alkyl optionally substituted with OR₁₈; amino or C_{1-C₅} branched or unbranched mono- or di-alkylamino optionally substituted with R₁₉;

R₂₀C(O)N(R₂₁)-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆CH₂C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

15 15 C₂₋₄ alkenyl substituted by R₂₃R₂₄NC(O)-;

C₂₋₄ alkynyl branched or unbranched carbon chain optionally partially or fully halogenated and optionally independently substituted with 0-2 oxo groups, pyrroldinyl, 20 pyrrolyl or one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

X is O;

and

25 R₂₃ and R₂₄ taken together optionally form imidazole, piperidine, morpholino, piperazine or a pyridinyl ring.

In yet another embodiment of the invention there is provided compounds of the
30 formula(I) as described immediately above, and wherein:

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl, benzothiophenyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indanyl, indolyl, indolinyl, indolonyl, indolinonyl, cyclopropanyl, cyclohexanyl, piperidinyl or tetrahydropyran, wherein G is substituted by one or more R₁, R₂ or R₃;

5

Ar is naphthyl;

L is a:

C₁₋₄ alkyl or alkynyl branched or unbranched carbon chain;

10 wherein one methylene group is optionally independently replaced by heteroatoms chosen from O, N and S(O)_m; and

wherein said L is optionally substituted with 0-2 oxo groups and one or more C₁₋₂ alkyl optionally substituted by one or more halogen atoms;

15 Q is:

phenyl, pyridinyl, pyrimidinyl, imidazolyl, tetrahydropyranyl, morpholino, thiomorpholino, thiomorpholino sulfoxide, piperidinyl, piperidinonyl or pentamethylene sulfoxide which are optionally substituted with one to three amino, mono- or di-(phenyl-

20 C₁₋₃ alkyl)amino, methyl, ethyl, methoxy, ethoxy, methoxymethyl or ethoxymethyl;

each R₁ is independently:

C₃₋₅ branched or unbranched alkyl optionally partially or fully halogenated, and
25 optionally substituted with phenyl substituted with 0 to 5 halogen, C₁₋₃ alkyl optionally partially or fully halogenated, hydroxy, cyano or C₁₋₃alkoxy optionally partially or fully halogenated;

30 cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, cyano, hydroxyC₁₋₃alkyl or phenyl;

or an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl wherein one ring methylene group is replaced by O; and

silyl containing three C₁₋₂ independently branched or unbranched alkyl groups optionally

5 partially or fully halogenated;

each R₃ is independently:

hydrogen, phenyl, pyridinyl, pyrimidinyl, pyrrolylidinyl, 2,5-pyrrolidin-dione,

10 imidazolyl, pyrazolyl, each of the aforementioned is optionally substituted with one to five C₁₋₃ alkyl optionally partially or fully halogenated, halogen, oxo, hydroxy, cyano or C₁₋₃ alkoxy optionally partially or fully halogenated;

C₁₋₃ alkyl or C₁₋₃ alkoxy which may optionally be partially or fully halogenated or

15 optionally substituted with R₁₇;

Cyclopropyloxy, cyclopentyloxy or cyclohexyloxy which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

20 C₀₋₃ branched or unbranched alkyl optionally substituted with OR₁₈;

amino or C_{1-C₃} branched or unbranched mono- or di-alkylamino optionally substituted with R₁₉;

R₂₀C(O)N(R₂₁)-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆CH₂C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

25

C₂₋₄ alkenyl substituted by R₂₃R₂₄NC(O)-; or

C₂₋₄ alkynyl substituted with pyrroldinyl or pyrrolyl;

and

R₂₃ and R₂₄ taken together optionally form morpholino.

30

In yet still another embodiment of the invention there is provided compounds of the formula(I) as described immediately above, and wherein

- G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl,
5 dihydrobenzofuranyl, indanyl, indolinyl, indolonyl, indolinonyl or cyclopropanyl,
wherein G is substituted by one or more R₁, R₂ or R₃;

Ar is 1-naphthyl;

10 L is:

O-CH₂-, O-CH₂CH₂, O-CH₂CH₂CH₂, O-CH₂CH₂(CH₃), O-CH₂(CH₃)CH₂, NHCH₂,
NHCH₂CH₂, NHCH₂CH₂CH₂, S(O)_mCH₂, S(O)_mCH₂CH₂, S(O)_mCH₂CH₂CH₂, CH₂CH₂,
CH₂CH₂CH₂, O-CH₂C(O),
HC≡C—CH₂ or HC≡C—CH₂O ;

15

each R₁ is independently:

C₃₋₅ branched or unbranched alkyl optionally partially or fully halogenated, and
optionally substituted with phenyl;

20

cyclopropyl, cyclopentanyl, cyclohexanyl or bicyclopentanyl optionally substituted with
one to three methyl groups optionally be partially or fully halogenated, CYANO,
hydroxymethyl or phenyl;

cyclopentyloxy or cyclohexyloxy which are optionally partially or fully halogenated;

25 2-tetrahydrofuranyl substituted by methyl; or
trimethylsilyl;

each R₃ is independently:

hydrogen, phenyl, pyridinyl, pyrimidinyl, pyrrolylidinyl, 2,5-pyrrolidin-dione, imidazolyl or pyrazolyl, wherein each of the aforementioned is optionally substituted with C₁₋₂ alkyl optionally partially or fully halogenated;

- 5 C₁₋₃ alkyl or C₁₋₃ alkoxy each optionally partially or fully halogenated or optionally substituted with diethylamino;

C₀₋₃ branched or unbranched alkyl optionally substituted with OR₁₈; amino or C_{1-C₃} branched or unbranched mono- or di-alkylamino optionally substituted
10 with R₁₉;

CH₃C(O)NH-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆CH₂C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

C₂₋₄ alkenyl substituted by R₂₃R₂₄NC(O)-; or

- 15 C₂₋₄ alkynyl substituted with pyrroldinyl or pyrrolyl;

R₂₃ and R₂₄ are H or R₂₃ and R₂₄ taken together optionally form morpholino; and
R₂₆ is morpholino.

20

In another embodiment of the invention there is provided of the formula(I) as described immediately above, and wherein

G is phenyl substituted by one or more R₁, R₂ or R₃;

- 25 and

L is:

O, NH, CH₂ or S(O)_m.

- 30 In yet another embodiment of the invention there is provided of the formula(I) as described in the fourth embodiment above, and wherein

G is phenyl or pyridinyl substituted by one or more R₁, R₂ or R₃;

Ar is 1-naphthyl;

5

L is:

C(O)CH₂- , >C(O), O, or CH₂;

each R₁ is independently:

10

C₃₋₅ branched or unbranched alkyl optionally partially or fully halogenated, and

each R₃ is independently:

15 hydrogen, C₁₋₃ alkyl or C₁₋₃ alkoxy each optionally be partially or fully halogenated or
optionally substituted with diethylamino;

CH₃C(O)NH-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

20 R₂₃ and R₂₄ are H or R₂₃ and R₂₄ taken together optionally form morpholino;
and

R₂₆ is alkylamino mono- or di-C₀₋₄ branched or unbranched.

25 In another embodiment of the invention there is provided of the formula(I) as described
immediately above, and wherein

G is pyridinyl

and

30 L is C(O)CH₂- , >C(O), O or CH₂.

Any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of formula (I) can exist in more than one tautomeric form. The invention includes all such tautomers.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C₁₋₄alkoxy" is a C₁₋₄alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, and butoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

The term "aroyl" as used in the present specification shall be understood to mean "benzoyl" or "naphthoyl".

- The term "carbocycle" shall be understood to mean an aliphatic hydrocarbon radical containing from three to twelve carbon atoms. Carbocycles include hydrocarbon rings containing from three to ten carbon atoms. These carbocycles may be either aromatic or non-aromatic ring systems. The non-aromatic ring systems may be mono- or polyunsaturated. Preferred carbocycles include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, decahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl.
- The term "heterocycle" refers to a stable nonaromatic 4-8 membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8-11 membered bicyclic heterocycle radical

which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Preferred heterocycles include but are not limited to, for example oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene sulfoxidyl, oxazolinyl, thiazolinyl, imidazolinyl, tetrahydropyridinyl, homopiperidinyl, pyrrolinyl, tetrahydropyrimidinyl, decahydroquinolinyl, decahydroisoquinolinyl, thiomorpholinyl, thiazolidinyl, dihydrooxazinyl, dihydropyranyl, oxocanyl, heptacanyl, thioxanyl, dithianyl.

The term "heteroaryl" shall be understood to mean an aromatic 5-8 membered monocyclic or 8-11 membered bicyclic ring containing 1-4 heteroatoms chosen from N, O and S. Such heteroaryls include: pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl, tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, benzoaxazolonyl, benzo[1,4]oxazin-3-onyl, benzodioxolyl, benzo[1,3]dioxol-2-onyl, tetrahydrobenzopyranyl, indolyl, indolinyl, indolonyl, indolinonyl, phthalimidyl.

The term "heteroatom" as used herein shall be understood to mean atoms other than carbon such as O, N, S and P.

The term "aryl" as used herein shall be understood to mean aromatic carbocycle or heteroaryl as defined herein.

Terms which are analogs of the above cyclic moieties such as aryloxy or heteroaryl amine shall be understood to mean an aryl, heteroaryl, heterocycle as defined above attached to its respective group.

As used herein, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.

The term "halogen" as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine.

- 5 The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the invention.
- 10 The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the formula(I) capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the formula(I).
- 15
- 20 Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of this invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C₁-C₄
- 25
- 30 alkyl)₄⁺ salts.

In addition, the compounds of this invention include prodrugs of compounds of the formula (I). Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a 5 prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound of formula (I), thereby imparting the desired pharmacological effect.

10

METHODS OF USE

In accordance with the invention, there are provided methods of using the compounds of the formula (I). The compounds of the invention effectively block inflammatory cytokine 15 production from cells. The inhibition of cytokine production is an attractive means for preventing and treating a variety of disorders associated with excess cytokine production, e.g., diseases and pathological conditions involving inflammation. Thus, the compounds of the invention are useful for the treatment of such conditions. These encompass chronic inflammatory diseases including, but not limited to, osteoarthritis, multiple 20 sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, systemic lupus erythematosus and insulin-dependent diabetes mellitus. The compounds of the invention can also be used to treat other disorders associated with the activity of elevated levels of proinflammatory cytokines such as 25 responses to various infectious agents and a number of diseases of autoimmunity such as rheumatoid arthritis, toxic shock syndrome, diabetes and inflammatory bowel diseases unrelated to those listed above are discussed in the Background of the Invention.

In addition, the compounds of the invention being inhibitors of cytokine production are expected to block inducible cyclooxygenase (COX-2) expression. COX-2 expression has 30 been shown to be increased by cytokines and it is believed to be the isoform of cyclooxygenase responsible for inflammation (M.K. O'Banion *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1992, 89, 4888.) Accordingly, the present novel compounds would be expected to exhibit efficacy against those disorders currently treated with COX inhibitors

such as the familiar NSAIDs. These disorders include acute and chronic pain as well as symptoms of inflammation and cardiovascular disease.

As discussed in the Background of the Invention, IL-8 plays a role in the influx of neutrophils into sites of inflammation or injury. Therefore, in a yet further aspect of the invention, the compounds of the invention may be useful in the treatment of diseases mediated predominantly by neutrophils such as stroke and myocardial infarction, alone or following thrombolytic therapy, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, hemodialysis, leukopheresis, granulocyte transfusion associated syndromes, and necrotizing enterocolitis.

For therapeutic use, the compounds of the invention may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

The compounds of this invention may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 5%, but more preferably at least about 20%, of a compound of formula (I)

(w/w) or a combination thereof. The optimum percentage (w/w) of a compound of formula(I) may vary and is within the purview of those skilled in the art. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

5

As mentioned above, dosage forms of the compounds of this invention include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and

15 requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 1-1000 mg/dose for a 70 kg patient.

Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, 20 lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

In order that this invention be more fully understood, the following examples are set 25 forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds. 30 Starting materials used in the scheme below are either commercially available or easily prepared from commercially available materials by those skilled in the art.

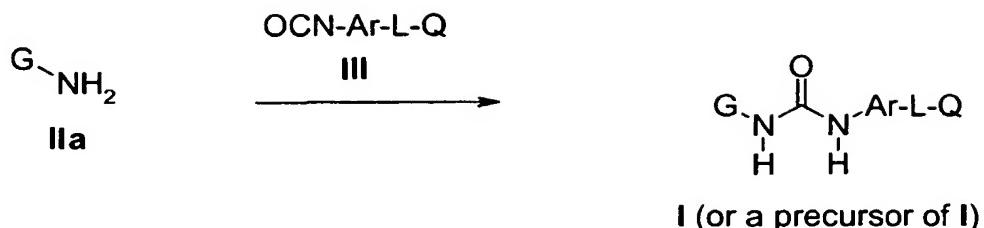
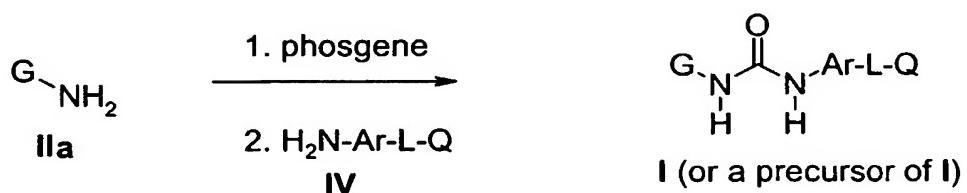
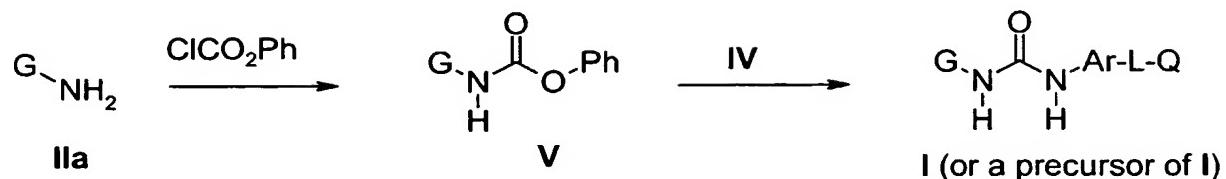
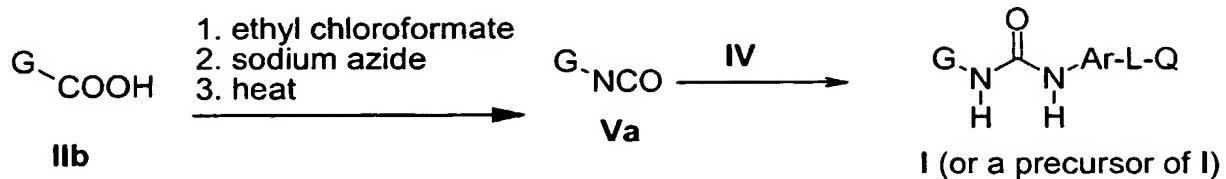
GENERAL SYNTHETIC METHODS

- 5 The invention additionally provides for methods of making the compounds of the formula (I). In all schemes "G" in the formulas shown below shall have the meaning of "G" in the formula (I) of the invention described hereinabove.

The compounds of the invention may be prepared by Method A, B, C or D as illustrated in Scheme I, preferably method C.

10

Scheme I

Method A**Method B****Method C****Method D**

In Method A, a mixture of an arylamine of formula IIa and an arylisocyanate of formula III is dissolved in a non-protic, anhydrous solvent such as THF, ether, toluene, dioxane or ethyl acetate. The preferred solvent is THF. The mixture is stirred at between 0 - 45°C, preferably at 25°C, for 2-24 h, and the volatiles are removed. Purification of the residue

can be accomplished by recrystallization from an appropriate solvent such as ethyl acetate/hexanes, ethyl acetate/methanol, THF/petroleum ether or ethanol/water or by silica gel chromatography, using for example, hexanes and ethyl acetate as eluents, providing the product of formula I or precursors thereof.

- 5 In Method B, an arylamine of formula IIa is dissolved in a halogenated solvent, such as methylene chloride, chloroform or dichloroethane. The preferred solvent is methylene chloride. The mixture is diluted with aqueous alkali, such as sodium bicarbonate or potassium carbonate, cooled in an ice bath and phosgene is added. The mixture is vigorously stirred for 5 – 30 min, with 10 min being preferable. The organic layer is
10 dried, with agents such as MgSO₄ or Na₂SO₄, and the volatiles removed to provide the corresponding isocyanate. The isocyanate and arylamine IV are mixed in a non-protic, anhydrous solvent such as THF, ether, toluene, dioxane, methylene chloride or ethyl acetate. The preferred solvent is THF. The mixture is stirred at between 0 - 45° C, preferably at 25° C, for 2 - 24 h, and the volatiles are removed. Purification of the residue
15 by recrystallization or by silica gel chromatography, as above, provides the product of formula I or precursors thereof.

In Method C, an arylamine of formula IIa is dissolved in a suitable halogenated solvent such as methylene chloride, chloroform or dichloroethane. The preferred solvent is methylene chloride. A suitable base such as triethylamine may be added, followed by an
20 alkyl or aryl chloroformate, such as *t*-butyl chloroformate or phenyl chloroformate (shown). The mixture is stirred at between 0 - 85° C, preferably at reflux temperature, for 2 - 24 h, and the volatiles are removed providing carbamate V. The carbamate and arylamine IV are mixed in a non-protic, anhydrous solvent such as THF, ether, toluene, dioxane, methylene chloride or ethyl acetate. The preferred solvent is THF. The mixture
25 is stirred at between 0 - 110° C, preferably at reflux temperature, for 2 - 24 h, and the volatiles are removed. Purification of the residue as above provides the product of formula I or precursors thereof.

In Method D, an aromatic carboxylic acid is dissolved in a non-protic solvent, such as THF or diethyl ether, and an inorganic base, such as triethyl amine is added and the mixture is cooled to -30-0°C, with the preferred temperature being -10°C. An alkyl chloroformate, such as ethyl chloroformate, is added dropwise and the resulting mixture 5 stirred at below room temperature, such as 0°C for 1-3 hours. A solution of sodium azide in water is added and the mixture stirred between 1-3 hours, diluted with toluene and the organic layer dried and reduced in volume. This mixture is heated at reflux for 1-4 hours, cooled to room temperature to give isocyanate (Vb) which can be reacted with amine (IV) to give product of formula I or precursors thereof.

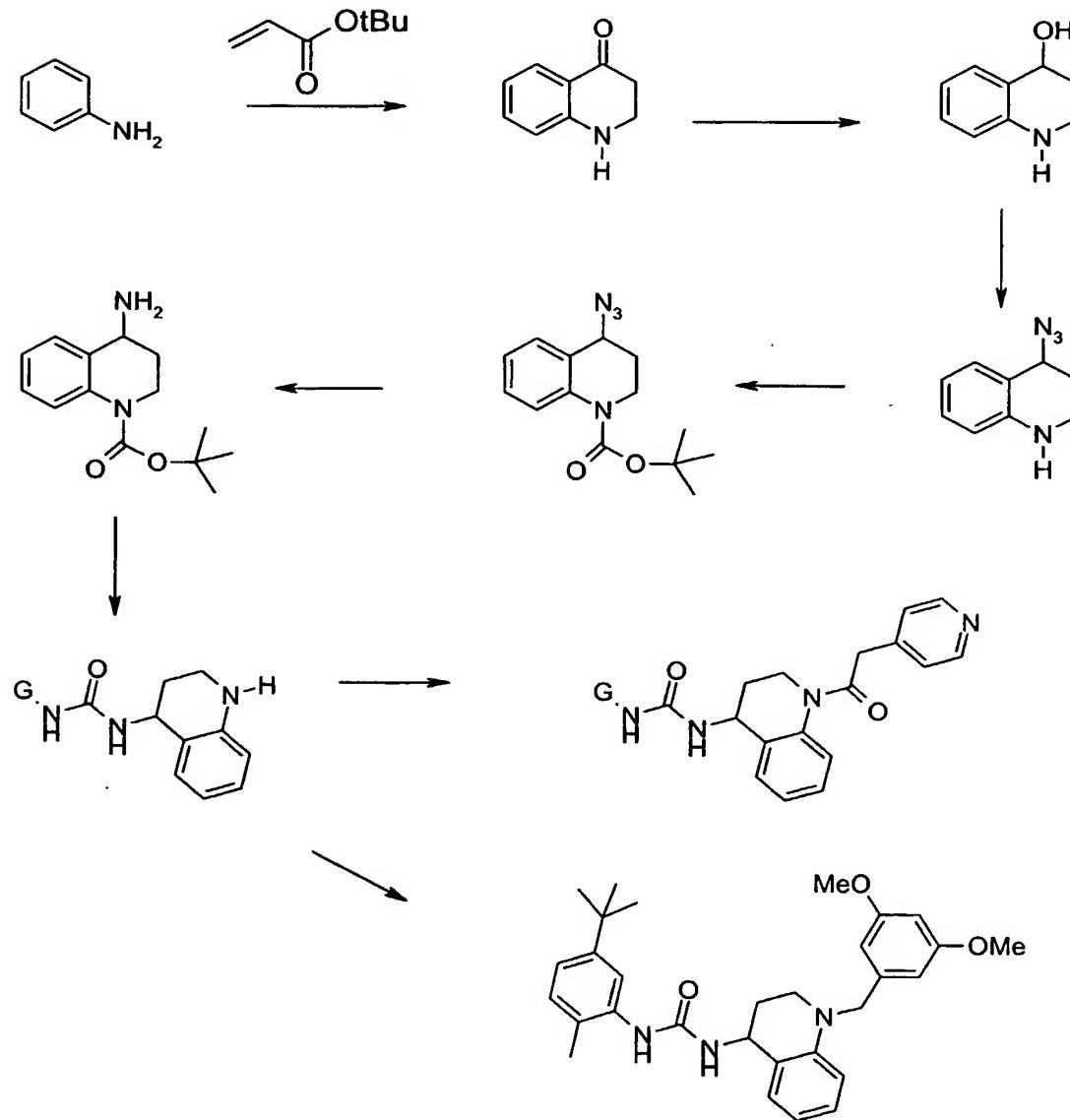
10 Method E describes a procedure by which one may obtain a product of formula (I) in which Ar is tetrahydroquinoline. Preparations of tetrahydroquinoline intermediates that may be used are known in the art (see for example C. Wang et al., *Biorg. Med. Chem. Lett.*, 1998, 2685; W.S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, 1952, 74, 4513; 15 P.D. Leeson et al., *Med. Chem. Res.*, 1991, 1, 64; A.L. Tokes, *Synth. Commun.*, 1989, 19, 2081; U. Gerlach et al., EP 0 857 724 A1, 05/02/1998). The following method is illustrative.

Aniline is reacted with an acrylate ester such as t-butyl acrylate, in a suitable solvent such 20 as acetic acid at reflux temperature. The product obtained is cyclized by heating under acidic conditions, such as heating in polyphosphoric acid to give the cyclic ketone. The ketone is reduced with a suitable reducing agent such as NaBH₄ to give the corresponding alcohol. The alcohol is converted to the amine by methods known in the art, for example, reaction with sodium azide under anhydrous acidic conditions in 25 ethereal solvent provides the azide. Protection of the tetrahydroquinoline nitrogen, for example by treatment with t-butyl dicarbonate under heating conditions affords the t-boc protected compound. Reaction under suitable reducing conditions, for example, Pd/charcoal and H₂ gas affords the t-boc protected 4-amino tetrahydroquinoline.
30 This may then be reacted using the desired Method B, C or D, to provide the urea. Deprotection, for example with trifluoroacetic acid, can be followed by further reaction to

add L-Q to provide the desired product of formula (I). For example, treatment with the desired acid, such as 4-pyridine acetic acid hydrochloride in the presence of a suitable carbodiimide coupling reagent provides an amide. Reaction with an arylaldehyde, for example 3,5-dimethoxybenzaldehyde in the presence of a suitable reducing agent such as Na(AcO)₃BH at room temperature affords the tetrahydroquinoline product in which L is a methylene bridge and Q is a substituted aryl group.

Method E

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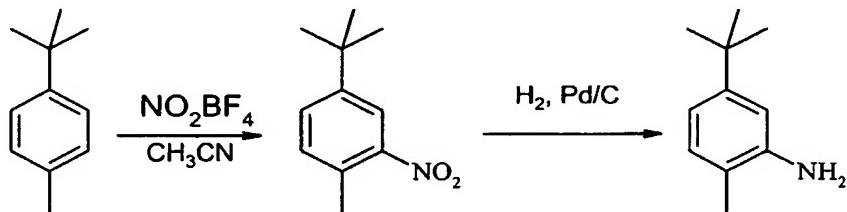


EXPERIMENTAL SECTION

5 Arylamine intermediates of formula IIa are either commercially available or may be prepared by methods known to those skilled in the art. Examples 1-5 (Methods F-J) are representative of procedures for preparing aryl amine or aryl isocyanate derivatives that may be used in Methods A-D. It will be obvious to those skilled in the art that other desired intermediates could be made by these methods by using appropriately substituted starting materials and intermediates.

10

Example 1 (Method F): Synthesis of 5-*tert*-butyl-2-methylaniline



15

To a solution of 4-*tert*-butyl toluene (5 g, 33.7 mmol) in acetonitrile (150 mL) at 0°C was added nitronium tetrafluoroborate (5.83 g, 40.5 mmol). After 30 min at room temperature, the reaction was diluted with water (50 mL) and extracted with ethyl acetate (3x30 mL). The combined organic extracts were washed with brine and dried (MgSO_4).

20

Removal of the volatiles *in vacuo* left a residue which was purified by flash chromatography using 10 % methylene chloride in petroleum ether as eluent.

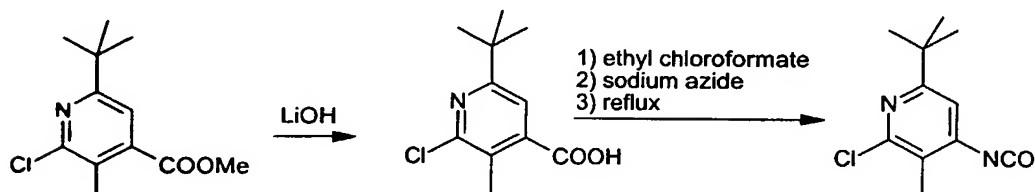
Concentration *in vacuo* of the product rich fractions provided 3.8 g of 4-*tert*-butyl-2-nitrotoluene.

25 4-*tert*-Butyl-2-nitrotoluene (200 mg, 1.1 mmol) was dissolved in DMF (10 mL). The catalyst (10% Pd/C, 5 mg) was added and the system was purged with argon then

exposed to H₂ (1 atm) for 12 h. The mixture was filtered over a pad of diatomaceous earth and the filtrate was diluted with water and extracted with ethyl acetate (3x10 mL). The combined organic extracts were washed with brine and dried (MgSO₄). Removal of the volatiles *in vacuo* provided the product 5-*tert*-butyl-2-methylaniline.

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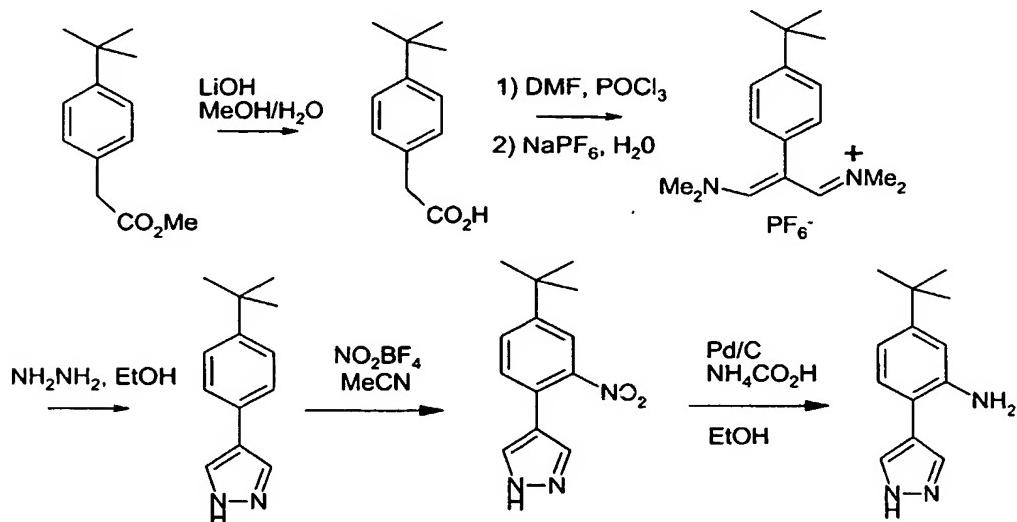
Example 2 (Method G): Synthesis of 6-*tert*-butyl-2-chloro-3-methylpyridin-yl-isocyanate



A mixture of 2-*t*-butyl-6-chloro-5-methylpyridine-4-carboxylic acid methyl ester (2.27 g, 9.39 mmol) and LiOH monohydrate (2.36 g, 56.3 mmol) in methanol (30 mL) and water (10 mL) was stirred at room temperature for 24 h. Removal of the volatiles *in vacuo* provided a residue which was purified by chromatography on silica gel using 5 % TFA in dichloromethane as the eluent. Concentration *in vacuo* of the product rich fractions provided the corresponding carboxylic acid (1.41 g, 66.3 %).

- 20 To a stirred solution of the above carboxylic acid (0.54 g, 2.36 mmol) and triethylamine (0.66 mL, 4.75 mmol) in THF (6 mL) at -10 °C ethyl chloroformate (0.34 mL, 3.51 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. A solution of sodium azide (0.40 g, 6.0 mmol) in water (2 mL) was added and stirring was continued for another 1 h. The mixture was extracted with toluene. The organic phase was separated, dried with sodium sulfate, and reduced in volume to 15 mL and heated at reflux for 2 h to provide 6-*tert*-butyl-2-chloro-3-methylpyridin-yl-isocyanate which was used without further purification.
- 25

Example 3 (Method H): Synthesis of 5-*t*-butyl-2-(1*H*-pyrazol-4-yl)aniline



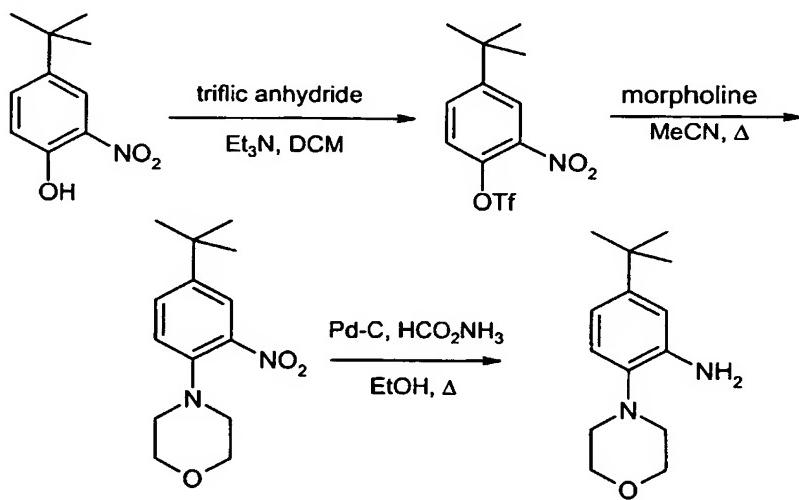
Methyl 4-*t*-butylphenylacetate (20 mmol) was dissolved in MeOH (160 mL) and treated with water (40 mL) and LiOH monohydrate (30 mmol). The reaction was allowed to stir at room temperature overnight. The volatiles were removed under reduced pressure and the remaining residue was diluted with water and neutralized to pH 4 with 1 N sulfuric acid. The resulting solids were filtered, washed with water and dried to leave 4-*t*-butylphenylacetic acid as an off-white solid (3.8 g, 99%).

Anhydrous DMF (139 mmol) was cooled to 0°C and treated with POCl₃ (79.6 mmol). After 5 min, 4-*t*-butylphenylacetic acid (19.9 mmol) was added and the mixture heated at 110°C for 2 h, cooled to room temperature and poured into a stirred solution of NaPF₆ (19.8 mmol) in water (200 mL). The solid was filtered, washed with water, and dried (7.8 g, 97%).

A mixture of the above salt (5 mmol) and hydrazine hydrate (5 mmol) in EtOH (50 mL) was heated at 90°C for 2 h and cooled to room temperature. The volatiles were removed under reduced pressure and the remaining residue diluted with ice water. The solids were filtered, washed with water and dried providing 4-(4-*t*-butylphenyl)pyrazole (973 mg, 97%).

- To a mixture of 4-(4-*t*-butylphenyl)pyrazole (0.5 mmol) in MeCN (2 mL) at 0°C was added NO₂BF₄ (0.6 mmol). The mixture was allowed to warm slowly to room temperature, stirred for 2 h and quenched with aqueous NaHCO₃. The volatiles were removed under reduced pressure. The residue was diluted with water and extracted with CH₂Cl₂. The organic layers were combined, dried (MgSO₄) and the volatiles removed *in vacuo*. Purification of the yellow oil by silica gel chromatography using 60% CH₂Cl₂ in ethyl acetate as the eluent and concentration *in vacuo* of the product rich fractions gave 4-(4-*t*-butyl-2-nitrophenyl)pyrazole as a yellow crystalline solid (71 mg, 58%).
- 5
- 10 A mixture of 4-(4-*t*-butyl-2-nitrophenyl)pyrazole (0.27 mmol), 10 % Pd/C (0.2 eq by weight of nitro compound) and NH₄CO₂H (2.7 mmol) in ethanol (3 mL) was stirred for 30 min and filtered through a bed of diatomaceous earth. The filtrate was concentrated under reduced pressure and the residue dissolved in water. The solid was filtered, washed with water and dried to give the product (54 mg, 93%).
- 15

Example 4 (Method I): Synthesis of 5-*tert*-butyl-2-(morpholin-4-yl)aniline

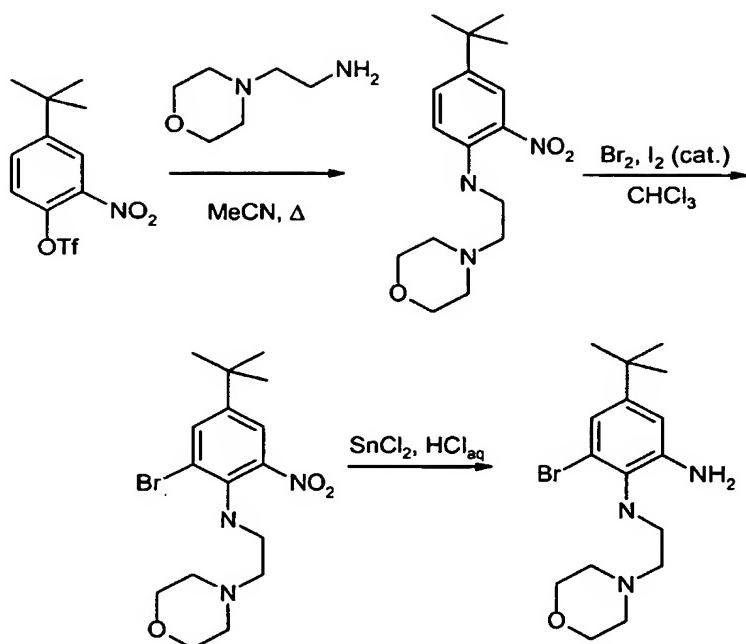


To a mixture of 2-nitro-4-tert-butyl phenol (5.4 g, 0.027 mol) and Et₃N (5.85 mL, 0.042 mol) in methylene chloride (100 mL) at 0°C, triflic anhydride (5.2 mL, 0.030 mol) was added *via* addition funnel. The reaction was stirred at room temperature for 2 days, diluted with water (10 mL) and extracted with ethyl acetate (3X10 mL). The combined 5 organic extracts were washed with brine and dried (MgSO₄). Removal of the volatiles *in vacuo* afforded 8.8 g (97% yield) of trifluoromethanesulfonic acid 4-tert-butyl-2-nitrophenyl ester, which crystallized in air.

A mixture of (400 mg, 1.2 mmol) of the above triflate and morpholine (314 mL, 3.6 10 mmol) in acetonitrile (10 mL) was stirred at 80°C for 4 h. Removal of the volatiles *in vacuo* afforded 315 mg, 97 % yield of 4-(4-tert-butyl-2-nitrophenyl)morpholine, as a yellow solid.

A mixture of the above nitro compound (320 mg, 1.2 mmol), ammonium formate (460 15 mg, 7.3 mmol) and 10% Pd/C (5 mg) in ethanol (20 mL) was stirred at 100°C for 1 h, cooled to room temperature and filtered. Removal of the volatiles *in vacuo* provided 260 mg (93%) of the title compound.

20 **Example 5: (Method J): Synthesis of 3-bromo-5-tert-butyl-2-[2-(morpholin-4-yl)ethylamino]aniline**



A mixture of trifluoromethanesulfonic acid 4-*tert*-butyl-2-nitro-phenyl ester (400 mg, 1.2 mmol) and N-(2-aminoethyl)morpholine (481 μ L, 3.7 mmol) in acetonitrile (10 mL) was stirred at 80°C for 4 h and cooled to room temperature. Removal of the volatiles *in vacuo* provided a residue that was purified by flash chromatography using 15% ethyl acetate in petroleum ether as eluent. Concentration *in vacuo* of the product-rich fractions provided 340 mg, 90% yield of the desired product, 4-*tert*-butyl-2-nitro-N-[2-(morpholin-4-yl)ethyl]aniline

To a solution of 4-*tert*-butyl-2-nitro-N-[2-(morpholin-4-yl)ethyl]aniline (240 mg, 0.8 mmol) in chloroform (1 mL) was added bromine (42 μ L, 0.8 mmol) and an iodine crystal. The mixture was stirred at room temperature for 1 h, diluted with water (10 mL) and extracted with ethyl acetate (3X10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Removal of the volatiles *in vacuo* afforded 300 mg, 99% yield of the desired aryl bromide, 6-bromo-4-*tert*-butyl-2-nitro-N-[2-(morpholin-4-yl)ethyl]aniline

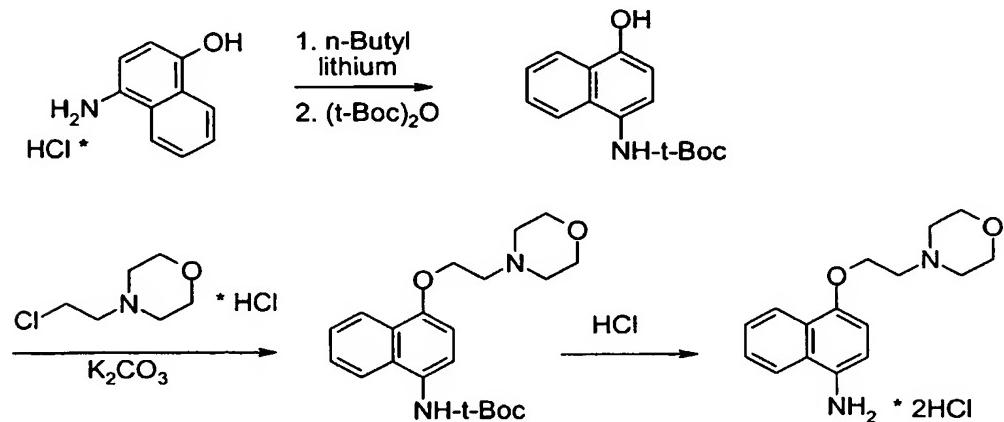
To a solution of 6-bromo-4-tert-butyl-2-nitro-N-[2-(morpholin-4-yl)ethyl]aniline (300 mg, 0.7 mmol) in 6 N HCl (15 mL) at 0°C was added stannous chloride (990 mg, 4.4 mmol), as a solution in 6N HCl (5 mL). The reaction was stirred for 1 h, basified with 20% potassium hydroxide and extracted with ethyl acetate (3X10 mL). The combined organic extracts were washed with brine and dried (MgSO_4). Removal of the volatiles *in vacuo* provided 200 mg, 72% yield, of the desired amine.

Examples 6-9 (Methods K-N) are representative procedures for the preparation of intermediates of formula IV which may be used in Methods B-D (Scheme I). The preparation of intermediates of formula IV may also be made with known starting materials and by methods known to those skilled in the art including those to be found in US serial number 09/484,638 incorporated herein by reference.

15

Example 6 (Method K): Synthesis of 1-amino-4-(2-morpholin-4-yl-ethoxy)naphthalene

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To a mixture of 4-amino-1-naphthol hydrochloride (172.1 g) in 750 mL anhydrous THF at -78°C was added dropwise over 60 min n-butyl lithium (490 mL of a 1.60 M solution in hexanes). After the addition was complete the mixture was allowed to warm to room

temperature and then cooled to -78°C and di-*tert*-butyl dicarbonate [$(\text{t-Boc})_2\text{O}$, 192 g] in 200 mL THF was added over 20 min. The mixture was slowly warmed to room temperature and stirred for 3 h and most of the volatiles removed in vacuo. The residue was diluted with ethyl acetate (1 L) and washed with water (2 X 200 mL) and brine (200 mL) and filtered through diatomaceous earth and dried (MgSO_4). Removal of the volatiles *in vacuo* provided the N-*t*-Boc protected derivative (226.1 g).

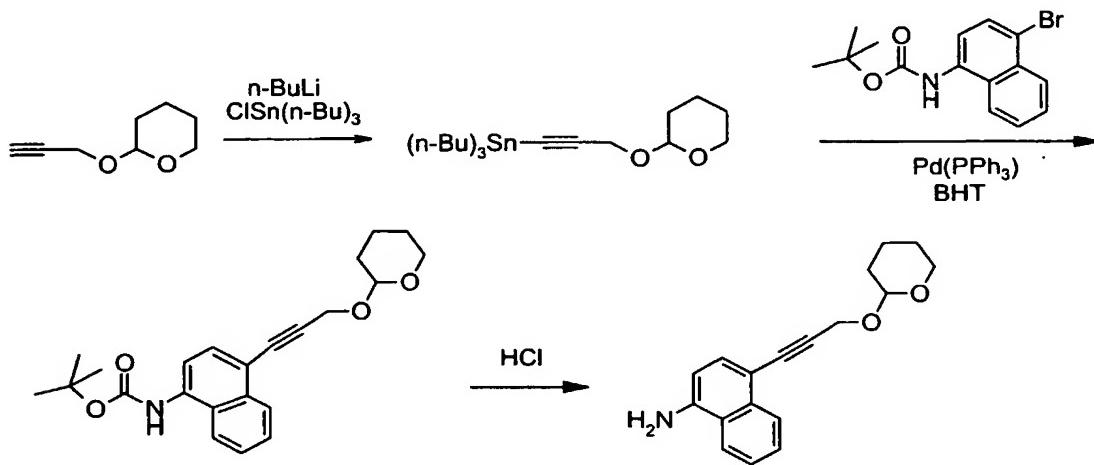
A mixture of the above N-*t*-Boc derivative (0.464 g), 4-(2-chloroethyl)morpholine hydrochloride (0.3435 g) and powdered potassium carbonate (0.93 g) was heated in acetonitrile (15 mL) at 80°C for 3 h, cooled to room temperature and diluted with ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO_4) and the volatiles removed *in vacuo*. Purification of the residue by flash chromatography using 12% hexanes in ethyl acetate as the eluent and concentration *in vacuo* of the product-rich fractions afforded N-*t*-Boc-4-[2-(morpholin-4-yl)ethoxy]naphth-1-yl-amine. A solution of this intermediate (0.511 g) and HCl (1 mL of 4M HCl in dioxane solution) in 5 mL dioxane was stirred at room temperature for 20 h. Removal of the volatiles *in vacuo* provided 4-[2-(morpholin-4-yl)ethoxy]naphth-1-yl-amine.

20 **Example 7 (Method L): Synthesis of 1-amino-4-(4-pyridinyl)oxynaphthalene.**



organic extracts were washed with HCl (2N), saturated aqueous NaHCO₃ and brine and dried (Na₂SO₄). Removal of the volatiles *in vacuo* afforded the product (0.5 g, 16 %).

5 **Example 8 (Method M): Synthesis of 1-amino-4-(3-(tetrahydropyran-2-yl-oxy)propyn-1-yl)naphthalene.**



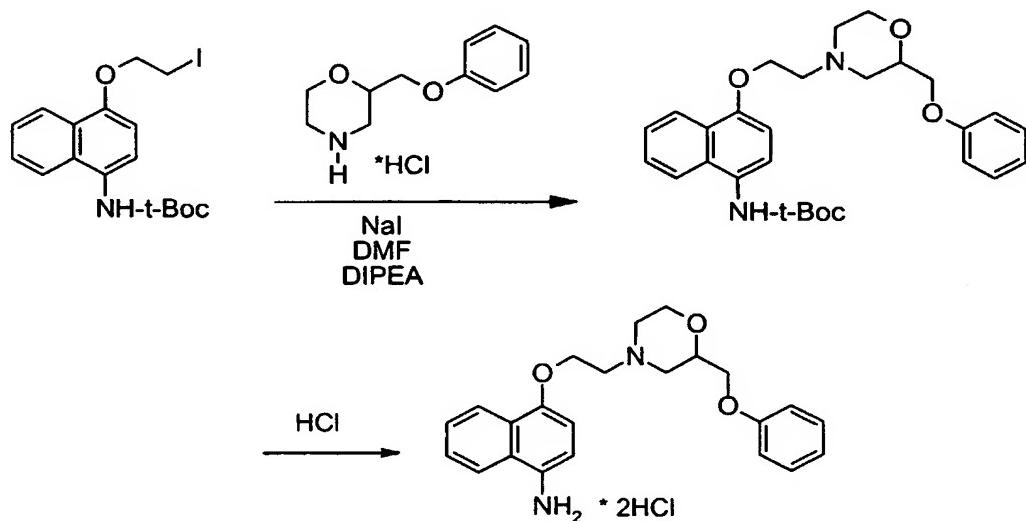
- 10 To a solution of tetrahydro-2-(2-propynyoxy)-2H-pyran in anhydrous THF at -78° C under inert atmosphere *n*-butyllithium (1.1 molar equivalents) was added *via* syringe. After 1 h stirring at -78° C, tributyltin chloride (1 molar equivalent) was added and the cooling bath was removed. After stirring at ambient temperature for 1 h the reaction mixture was quenched with saturated NH₄Cl solution and extracted with ethyl ether. The
15 combined ethereal extracts were washed with brine and dried (MgSO₄). After filtration all volatiles were removed *in vacuo* to produce the alkynyl tri-*n*-butylstannane as a yellow oil which was used without further purification.

- A mixture of N-*t*-Boc-4-bromonaphthylamine and the above alkynyl stannane (1.5 molar
20 equivalents) and BHT (20% weight equivalent) in toluene were heated at reflux under inert atmosphere and treated with palladium (0) tetrakis-(triphenylphosphine) (0.1 molar equivalent) When the reaction was complete, as judged by the color change to black, it was cooled to room temperature. An aqueous solution of KF (5M) was added and the

mixture was stirred vigorously for 6 h and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried (MgSO_4), filtered and all volatiles were removed *in vacuo*. Purification of the residue by column chromatography afforded the N-*t*-Boc intermediate. Removal of the N-*t*-Boc protecting group with HCl in dioxane provided the amino intermediate.

Example 9 (Method N): Synthesis of 1-amino-4-[2-(2-phenoxyethylmorpholin-4-yl)-ethoxy]naphthalene dihydrochloride:

10



15 A solution of 2-phenoxymorpholine hydrochloride (0.098 g), N,N-di-*iso*-propylethylamine (DIPEA) (149 uL), sodium iodide (0.32 g) and 1-N-Boc-4-(2-iodoethoxy)naphthylamine (0.176 g) in anhydrous DMF (1.5 mL) was heated at 40° C overnight, cooled to room temperature and diluted with ethyl acetate and water. The organic layer was washed with water and brine and dried (MgSO_4). Removal of the volatiles *in vacuo* provided a residue that was purified by silica gel chromatography using 20 33% hexanes in ethyl acetate as the eluent. Concentration of the product rich fractions *in vacuo* furnished 1-N-Boc-4-[2-(2-phenoxyethylmorpholin-4-yl)-ethoxy]naphthylamine.

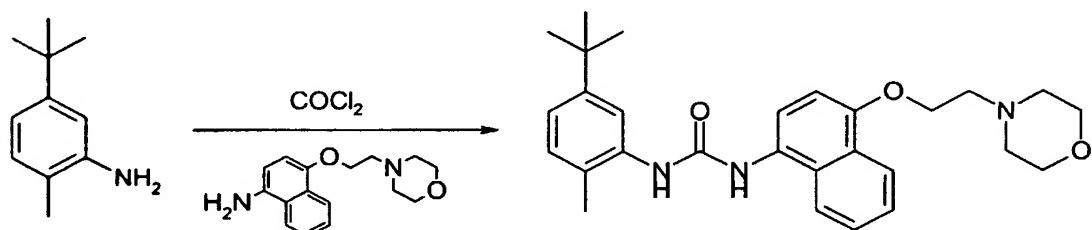
To a solution of the above *t*-Boc protected naphthylamine (0.18 g) in dioxane (1 mL) 25 was added HCl (0.47 mL of a 4N HCl in dioxane solution) and the mixture stirred

overnight at room temperature, diluted with ether and cooled. The solid was filtered and washed with ether and dried to provide 1-amino-4-[2-(2-phenoxyethylmorpholin-4-yl)ethoxy]naphthalene dihydrochloride.

5

Urea bond formation by Methods A-D is generally known in the art. A representative example is given below.

10 **Example 10 (Method B): 1-[5-tert-butyl-2-methylphenyl]-3-[4-(2-morpholin-4-yl)-ethoxy]-naphthalen-1-yl]-urea**



15

4-[2-(Morpholin-4-yl)ethoxy]naphthalen-1-yl-amine (280 mg, 1.0 mmol) was dissolved in dichloromethane (15 mL). An equal volume of sat. aqueous sodium bicarbonate was added, and the biphasic solution was cooled to 0 °C. During the addition of phosgene (1.93 M in toluene, 1.0 mL), stirring was stopped. Immediately afterward, stirring was resumed for 15 min with the reaction mixture at 0 °C. The layers were separated, the organics were dried over solid magnesium sulfate and concentrated to approximately 5 mL of solution. 5-tert-Butyl-2-methylaniline (150 mg, 0.9 mmol) in dichloromethane (5 mL) was added, and the reaction mixture was stirred for 17 h at ambient temperature. The desired compound was obtained after treatment of the reaction mixture with petroleum ether and filtering to collect the precipitate (180 mg, 42%).

30

From the synthetic schemes and the example described above, the following representative compounds of the formula(I) can be made:

TABLE I

| Structure | Chemical Name |
|-----------|---|
| | 1-(2-Methoxy-5-pentafluoroethyl-phenyl)-3-{4-[2-(tetrahydro-pyran-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(2-Methoxy-5-trifluoromethyl-pyridin-3-yl)-3-{4-[(pyridin-4-ylmethyl)-amino]-naphthalen-1-yl}-urea |
| | 1-(2-Methoxy-5-trimethylsilyanyl-phenyl)-3-[4-(pyridin-4-ylmethoxy)-naphthalen-1-yl]-urea |
| | 1-(3-tert-Butyl-phenyl)-3-[4-(3-pyridin-3-yl-propoxy)-naphthalen-1-yl]-urea |
| | 1-(4-Methoxy-biphenyl-3-yl)-3-{4-[2-(tetrahydro-pyran-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(4-tert-Butyl-biphenyl-2-yl)-3-[4-(pyridin-4-ylmethoxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-hydroxy-phenyl)-3-[4-(2-thiomorpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxy-3-propyl-phenyl)-3-[4-(3-morpholin-4-yl-propyl)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(1-methyl-2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-yl-2-oxo-ethoxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxy-phenyl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |

| | |
|--|--|
| | 1-(5-tert-Butyl-2-methyl-benzoxazol-7-yl)-3-{4-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-naphthalen-1-yl}-urea |
| | 1-(5-tert-Butyl-2-methyl-phenyl)-3-{4-[2-(3,4-dimethoxy-phenyl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(5-tert-Butyl-2-morpholin-4-yl-phenyl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-[4-(2-morpholin-4-yl-propoxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-pyrrolidin-1-yl-phenyl)-3-{4-[2-(2-methoxymethyl-morpholin-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-3-{4-[2-(2,6-dimethyl-morpholin-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(5-tert-Butyl-4'-dimethylamino-biphenyl-3-yl)-3-[4-(3-piperidin-1-yl-prop-1-ynyl)-naphthalen-1-yl]-urea |
| | 1-(6-Methoxy-3,3-dimethyl-indan-5-yl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-(6-tert-Butyl-2-chloro-3-methyl-pyridin-4-yl)-3-{4-[2-(tetrahydro-pyran-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(6-tert-Butyl-benzo[1,3]dioxol-4-yl)-3-[4-(1-methyl-2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-(7-Methoxy-1,4,4-trimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-3-{4-[2-(1-oxo-tetrahydro-1H-thiophen-3-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(7-tert-Butyl-2,4-dimethyl-benzoxazol-5-yl)-3-{4-[3-(tetrahydro-pyran-3-yloxy)-prop-1-ynyl]-naphthalen-1-yl}-urea |

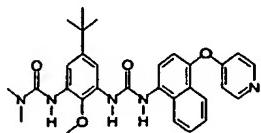
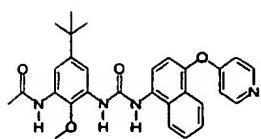
| | |
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| | 1-[2-Methoxy-5-(1-methyl-cyclohexyl)-phenyl]-3-{4-[3-(4-oxo-piperidin-1-yl)-prop-1-ynyl]-naphthalen-1-yl}-urea |
| | 1-[2-Methoxy-5-(1-methyl-cyclopropyl)-phenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-[2-Methoxy-5-(1-phenyl-cyclopropyl)-phenyl]-3-[4-(2-morpholin-4-yl-propoxy)-naphthalen-1-yl]-urea |
| | 1-[2-Methoxy-5-(2-methyl-tetrahydro-furan-2-yl)-phenyl]-3-[4-(2-thiomorpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-[2-Methoxy-5-(3-trifluoromethyl-bicyclo[1.1.1]pent-1-yl)-phenyl]-3-[4-(2-pyridin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-[3-Bromo-5-tert-butyl-2-(2-morpholin-4-yl-ethylamino)-phenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-[3-tert-Butyl-5-(1-methyl-1H-imidazol-4-yl)-phenyl]-3-[4-(2-morpholin-4-yl-2-oxo-ethoxy)-naphthalen-1-yl]-urea |
| | 1-[3-tert-Butyl-5-(2-pyrrolidin-1-yl-ethyl)-phenyl]-3-[4-(pyridin-4-ylmethoxy)-naphthalen-1-yl]-urea |
| | 1-[3-tert-Butyl-5-(3-pyrrolidin-1-yl-prop-1-ynyl)-phenyl]-3-[4-(2-pyridin-4-yl-ethyl)-naphthalen-1-yl]-urea |
| | 1-[4-(2-Imidazol-1-yl-ethoxy)-naphthalen-1-yl]-3-(4-methyl-biphenyl-3-yl)-urea |
| | 1-[4-(2-Imidazol-1-yl-ethoxy)-naphthalen-1-yl]-3-[2-methoxy-5-(1-methyl-1-phenyl-ethyl)-phenyl]-urea |
| | 1-[5-(1-Cyano-cyclopropyl)-2-methoxy-phenyl]-3-[4-(2-morpholin-4-yl-propoxy)-naphthalen-1-yl]-urea |

| | |
|--|--|
| | 1-[5-(1-Hydroxymethyl-cyclopropyl)-2-methoxy-phenyl]-3-{4-[(pyridin-4-ylmethyl)-amino]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-1-(2-diethylamino-ethyl)-2-oxo-1,2-dihydro-pyridin-3-yl]-3-{4-[3-(2-methoxymethyl-morpholin-4-yl)-prop-1-ynyl]-naphthalen-1-yl}-urea |
| | 1-(5-tert-Butyl-2-phenoxy-phenyl)-3-{4-[2-(2,6-dimethyl-morpholin-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-2-(1H-pyrazol-4-yl)-phenyl]-3-[4-(2-morpholin-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-2-(2,5-dioxo-pyrrolidin-1-yl)-phenyl]-3-{4-[2-(tetrahydro-pyran-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-2-(2-methyl-pyrimidin-5-yl)-phenyl]-3-{4-[2-(1-oxo-tetrahydro-1H-thiophen-3-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-{4-[2-(1-oxo-thiomorpholin-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-2-(2-morpholin-4-yl-2-oxo-ethoxy)-phenyl]-3-{4-[6-(2-pyridin-4-yl-ethyl)-pyridazin-3-yl]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-2-(2-morpholin-4-yl-2-oxo-ethylamino)-phenyl]-3-{4-[3-(tetrahydro-pyran-3-yloxy)-prop-1-ynyl]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-2-(6-methyl-pyridin-3-yl)-phenyl]-3-[4-(2-pyridin-2-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-2-methoxy-3-(3-morpholin-4-yl-3-oxo-propenyl)-phenyl]-3-{4-[2-(2,6-dimethyl-morpholin-4-yl)-ethoxy]-naphthalen-1-yl}-urea |
| | 1-[5-tert-Butyl-3-(2-diethylamino-ethoxy)-2-methoxy-phenyl]-3-[4-(2-thiomorpholin-4-yl-ethoxy)-naphthalen-1-yl}-urea |

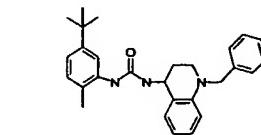
| | |
|--|---|
| | 1-[5-tert-Butyl-3-(2-pyrrolidin-1-yl-ethyl)-benzofuran-7-yl]-3-[4-(pyridin-4-ylmethoxy)-naphthalen-1-yl]-urea |
| | 1-[6-tert-Butyl-4-(2-dimethylamino-ethyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl]-3-[4-(3-piperidin-1-yl-prop-1-ynyl)-naphthalen-1-yl]-urea |
| | 1-{4-[2-(2,6-Dimethyl-morpholin-4-yl)-ethoxy]-naphthalen-1-yl}-3-[5-(1,1-dimethyl-propyl)-2-methoxy-phenyl]-urea |
| | 1-{4-[2-(3,4-Dimethoxy-phenyl)-ethoxy]-naphthalen-1-yl}-3-(3-methyl-naphthalen-2-yl)-urea |
| | 1-{4-[3-(2-Methoxymethyl-morpholin-4-yl)-prop-1-ynyl]-naphthalen-1-yl}-3-(3-methoxy-naphthalen-2-yl)-urea |
| | 1-{5-tert-Butyl-2-methoxy-3-[2-(1-methyl-piperidin-4-yloxy)-ethyl]-phenyl}-3-[4-(3-pyridin-3-yl-propoxy)-naphthalen-1-yl]-urea |
| | 2-[4-tert-Butyl-2-(3-{4-[2-(1-oxo-tetrahydro-thiophen-3-yl)-ethoxy]-naphthalen-1-yl}-ureido)-phenoxy]-N-methyl-acetamide |
| | 3-(3-tert-Butyl-5-{3-[4-(3-piperidin-1-yl-prop-1-ynyl)-naphthalen-1-yl]-ureido}-phenyl)-N,N-dimethyl-propionamide |
| | 3-(5-tert-Butyl-2-methoxy-3-{3-[4-(2-pyridin-2-yl-ethoxy)-naphthalen-1-yl]-ureido}-phenyl)-acrylamide |
| | 4-tert-Butyl-2-{3-[4-(3-morpholin-4-yl-prop-1-ynyl)-naphthalen-1-yl]-ureido}-benzamide |
| | N-(3-tert-Butyl-5-{3-[4-(2-morpholin-4-yl-propoxy)-naphthalen-1-yl]-ureido}-phenyl)-2-morpholin-4-yl-acetamide |
| | N-(4-tert-Butyl-2-{3-[4-(3-morpholin-4-yl-propyl)-naphthalen-1-yl]-ureido}-phenyl)-2-morpholin-4-yl-acetamide |

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| | N-[4-tert-Butyl-2-(3-{4-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-naphthalen-1-yl}-ureido)-phenyl]-acetamide |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-aminopyridin-4-yl-oxy)-naphthalen-1-yl]-urea, |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-(methylamino)pyridin-4-yl-oxy)-naphthalen-1-yl]-urea, |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-(phenylamino)pyridin-4-yl-oxy)-naphthalen-1-yl]-urea, |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-(1-phenylethylamino)pyridin-4-yl-oxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-(1-phenylethylamino)pyrimid-4-yl-methyl)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-(1-phenylethylamino)pyridin-4-yl-methyl)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-(1-phenylethylamino)pyridin-4-yl-thio)-naphthalen-1-yl]-urea |
| | 1-[5-tert-butyl-2-methylphenyl]-3-[4-(4-pyridinyloxy)-naphthalen-1-yl]-urea |
| | 1-[5-tert-butyl-2-methylphenyl]-3-[4-(3-pyridinyloxy)-naphthalen-1-yl]-urea |
| | 1-[5-tert-butyl-2-methoxyphenyl]-3-[4-(2-(2-phenoxyethyl)morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |
| | 1-[5-tert-butyl-2-methylphenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea |

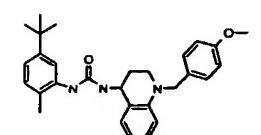
| | |
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| | 1-[3-acetamido-5-trifluoromethyl-2-methylthiophenyl]-3-[4-(3-pyridinyloxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-methoxy-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(3,4-dimethoxyphenyl-oxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(4-methylsulfonyl-oxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-methyl-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(1H-pyrido[2,3-b]pyridin-4-yl-oxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(1H-pyrazolo[2,3-b]pyridin-4-yl-oxy)-naphthalen-1-yl]-urea |
| | 1-(5-tert-Butyl-2,3-dimethoxyphenyl)-3-[4-(2-methoxy-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea |
| | 5-tert-Butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}benzamide |
| | Morpholine-4-carboxylic acid (5-tert-butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}phenyl)amide |



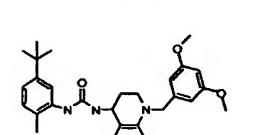
1-(1-Benzyl-1,2,3,4-tetrahydro-quinolin-4-yl)-3-(5-tert-butyl-2-methyl-phenyl)-urea



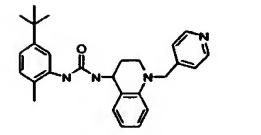
1-(5-tert-Butyl-2-methyl-phenyl)-3-[1-(4-methoxy-benzyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-urea



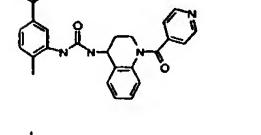
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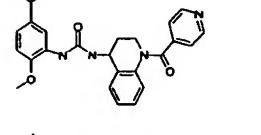
1-(5-tert-Butyl-2-methyl-phenyl)-3-(1-pyridin-4-ylimethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-urea



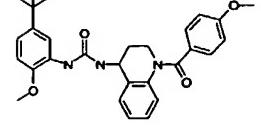
1-(5-tert-Butyl-2-methyl-phenyl)-3-[1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-urea



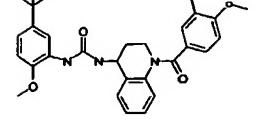
1-(5-tert-Butyl-2-methoxy-phenyl)-3-[1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-urea

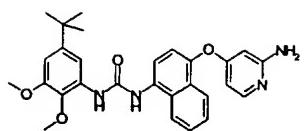


1-(5-tert-Butyl-2-methoxy-phenyl)-3-[1-(4-methoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-urea

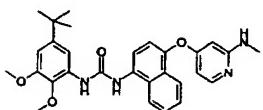


1-(5-tert-Butyl-2-methoxy-phenyl)-3-[1-(3,4-dimethoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-urea

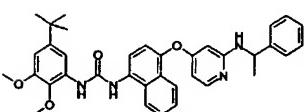




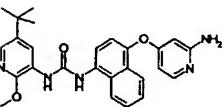
1-[4-(2-Amino-pyridin-4-yloxy)-naphthalen-1-yl]-3-(5-tert-butyl-2,3-dimethoxy-phenyl)-urea



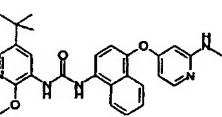
1-(5-tert-Butyl-2,3-dimethoxy-phenyl)-3-[4-(2-methylamino-pyridin-4-yloxy)-naphthalen-1-yl]-urea



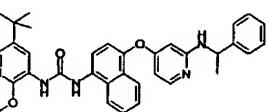
1-(5-tert-Butyl-2,3-dimethoxy-phenyl)-3-{4-[2-(1-phenyl-ethylamino)-pyridin-4-yloxy]-naphthalen-1-yl}-urea



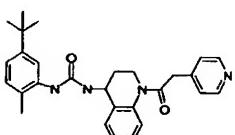
1-[4-(2-Amino-pyridin-4-yloxy)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-pyridin-3-yl)-urea



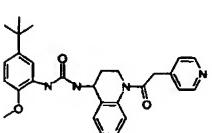
1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(2-methylamino-pyridin-4-yloxy)-naphthalen-1-yl]-urea



1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-{4-[2-(1-phenyl-ethylamino)-pyridin-4-yloxy]-naphthalen-1-yl}-urea



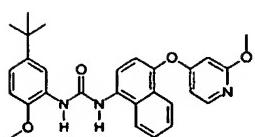
1-(5-tert-Butyl-2-methylphenyl)-3-[1-(2-pyridin-4-yl-acetyl)-1,2,3,4-tetrahydroquinolin-4-yl]-urea



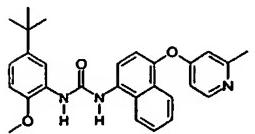
1-(5-tert-Butyl-2-methoxyphenyl)-3-[1-(2-pyridin-4-yl-acetyl)-1,2,3,4-tetrahydroquinolin-4-yl]-urea

and the pharmaceutically acceptable salts thereof.

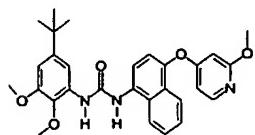
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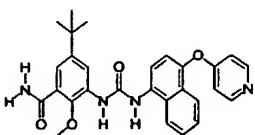
1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-methoxy-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea



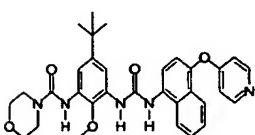
1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-methyl-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea



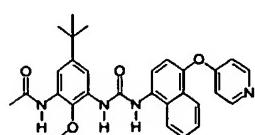
1-(5-tert-Butyl-2,3-dimethoxyphenyl)-3-[4-(2-methoxy-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea



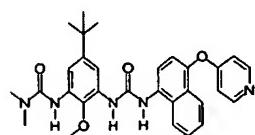
5-tert-Butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}benzamide



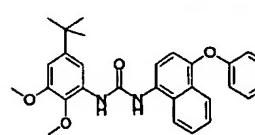
Morpholine-4-carboxylic acid (5-tert-butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}phenyl)amide



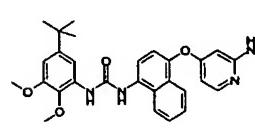
N-(5-tert-Butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}phenyl)acetamide



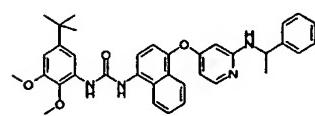
3-(5-tert-Butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}phenyl)-1,1-dimethylurea



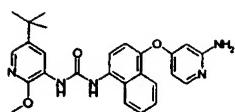
1-[4-(2-Amino-pyridin-4-yloxy)-naphthalen-1-yl]-3-(5-tert-butyl-2,3-dimethoxy-phenyl)-urea



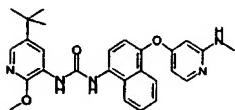
1-(5-tert-Butyl-2,3-dimethoxy-phenyl)-3-[4-(2-methylamino-pyridin-4-yloxy)-naphthalen-1-yl]-urea



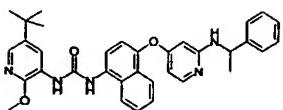
1-(5-tert-Butyl-2,3-dimethoxy-phenyl)-3-[4-[2-(1-phenyl-ethylamino)-pyridin-4-yloxy]-naphthalen-1-yl]-urea



1-[4-(2-Amino-pyridin-4-yloxy)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-pyridin-3-yl)-urea



1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(2-methylamino-pyridin-4-yloxy)-naphthalen-1-yl]-urea



1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-{4-[2-(1-phenyl-ethylamino)-pyridin-4-yloxy]-naphthalen-1-yl}-urea

and the pharmaceutically acceptable salts thereof.

5

The following compounds found in Table I were evaluated, all had IC₅₀ < 10 uM in the “Inhibition of TNF Production in THP Cells” assay described below:

- 10 1-(5-tert-Butyl-2-methylphenyl)-3-[4-(2-aminopyridin-4-yl-oxy)naphthalen-1-yl]urea;
- 11 1-(5-tert-Butyl-2-morpholin-4-yl-phenyl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea;
- 15 1-[3-Bromo-5-tert-butyl-2-(2-morpholin-4-yl-ethylamino)-phenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea;
- 16 1-[5-tert-butyl-2-methylphenyl]-3-[4-(4-pyridinyloxy)-naphthalen-1-yl]-urea;
- 20 1-[5-tert-butyl-2-methylphenyl]-3-[4-(3-pyridinyloxy)-naphthalen-1-yl]-urea;
- 21 1-[5-tert-butyl-2-methoxyphenyl]-3-[4-(2-(2-phenoxyethyl)morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea
and
- 25 1-[5-tert-butyl-2-methylphenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea.

30

ASSESSMENT OF BIOLOGICAL PROPERTIES

Inhibition of TNF Production in THP Cells

5 The inhibition of cytokine production can be observed by measuring inhibition of TNF α in lipopolysaccharide stimulated THP cells (for example, see W. Prichett *et al.*, 1995, *J. Inflammation*, 45, 97). All cells and reagents were diluted in RPMI 1640 with phenol red and L-glutamine, supplemented with additional L-glutamine (total: 4 mM), penicillin and streptomycin (50 units/ml each) and fetal bovine serum (FBS, 3%) (GIBCO, all conc. final). Assay was performed under sterile conditions; only test compound preparation was nonsterile. Initial stock solutions were made in DMSO followed by dilution into RPMI 1640 2-fold higher than the desired final assay concentration. Confluent THP.1 cells (2x10⁶ cells/mL, final conc.; American Type Culture Company, Rockville, MD) were added to 96 well polypropylene round bottomed culture plates (Costar 3790; sterile)

10 containing 125 μ L test compound (2 fold concentrated) or DMSO vehicle (controls, blanks). DMSO concentration did not exceed 0.2% final. Cell mixture was allowed to preincubate for 30 min, 37°C, 5% CO₂ prior to stimulation with lipopolysaccharide (LPS; 1 μ g/mL final; Siga L-2630, from E.coli serotype 0111.B4; stored as 1 mg/mL stock in endotoxin screened distilled H₂O at -80°C). Blanks (unstimulated) received H₂O vehicle; final incubation volume was 250 μ l. Overnight incubation (18 - 24 hr) proceeded as described above. Assay was terminated by centrifuging plates 5 min, room temperature, 1600 rpm (400 x g); supernatants were transferred to clean 96 well plates and stored -80°C until analyzed for human TNF α by a commercially available ELISA kit (Biosource #KHC3015, Camarillo, CA). Data was analyzed by non-linear regression (Hill equation) to generate a dose response curve using SAS Software System (SAS institute, Inc., Cary, NC). The calculated IC₅₀ value is the concentration of the test compound that caused a 50% decrease in the maximal TNF α production.

15

20

25

Inhibition of other cytokines

By similar methods using peripheral blood monocytic cells, appropriate stimuli, and

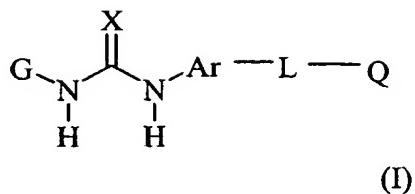
commercially available ELISA kits (or other method of detection such as

- 5 radioimmunoassay), for a particular cytokine, inhibition of IL-1 β , GM-CSF, IL-6 and IL-8 can be demonstrated (for example, see J.C. Lee *et al.*, 1988, *Int. J. Immunopharmacol.*, 10, 835).

What is claimed is:

1. A Compound of the formula (I):

5



wherein:

10

G is:

an aromatic C₆₋₁₀ carbocycle or a nonaromatic C₃₋₁₀ carbocycle saturated or unsaturated;
a 6-10 membered heteroaryl containing 1 or more heteroatoms chosen from O,N and S;
or

15 a 5-8 membered monocyclic heterocycle or a 8-11 membered bicyclic heterocycle, each containing one or more heteroatoms chosen from O,N and S;
wherein G is substituted by one or more R₁, R₂ or R₃;

Ar is:

20

phenyl, naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl,
dihydrobenzofuranyl, dihydrobenzothienyl, indolenyl, benzothiophenyl,
tetrahydroisoquinolinyl, benzimidazolyl, benzofuranyl, indanyl, indenyl or indolyl each
optionally substituted by one or more R₄ or R₅ groups;

25

L is a:

C₁₋₁₀ saturated or unsaturated branched or unbranched carbon chain;
wherein one or more methylene groups are optionally independently replaced by
30 heteroatoms chosen from O, N and S(O)_m; and

wherein said L is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

Q is:

5

phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, imidazolyl, benzimidazolyl, furanyl, thienyl, pyranyl, naphthyridinyl, pyrazinyl, pyrazolyl, triazolyl, tetrazolyl, pyrazolo[3,4-b]pyrimidinyl, purinyl, pyrrolo[2,3-b]pyridinyl, pyrazolo[3,4-b]pyridinyl, tubercidinyl, oxazo[4,5-b]pyridinyl and imidazo[4,5-b]pyridinyl, which are optionally substituted with one to three C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, amino, mono- or di-(C₁₋₃ alkyl)amino, mono- or di-(phenyl-C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, phenyl- C₁₋₃-alkoxy or phenylamino wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkyl or C₁₋₆ alkoxy;

15 tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxide, thiomorpholino sulfone, piperazinyl, piperidinyl, piperidinonyl, tetrahydropyrimidonyl, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide or tetramethylene sulfone which 20 are optionally substituted with one to three C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl or C₁₋₃ alkoxy-C₁₋₃ alkyl;

C₁₋₆ alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to C₁₋₃ alkyl or C₁₋₅ alkoxyalkyl, phenylamino, wherein the phenyl ring is 25 optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m or phenyl-S(O)_m wherein the phenyl ring is optionally substituted with one to two halogen, C₁₋₆ alkoxy, hydroxy or mono- or di-(C₁₋₃ alkyl)amino;

30 each R₁ is independently:

- C₃₋₁₀ branched or unbranched alkyl optionally partially or fully halogenated, and
optionally substituted with one to three C₃₋₁₀ cycloalkyl, hydroxy, phenyl, naphthyl ,
pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl,
furyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted
5 with 1 to 5 halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or
fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, hydroxy, cyano, C₁₋₃ alkoxy which
is optionally partially or fully halogenated and NH₂C(O) or mono- or
di(C₁₋₃)alkylaminocarbonyl;
- 10 cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl,
bicyclohexanyl or bicycloheptanyl, which are optionally partially or fully halogenated
and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully
halogenated, cyano, hydroxyC₁₋₃alkyl or aryl; or an analog of cyclopropyl, cyclobutyl,
cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or
15 bicycloheptanyl wherein one to three ring methylene groups are replaced independently
by O, S(O)_m, CHOH, >C=O, >C=S or NH;
- C₃₋₁₀ branched or unbranched alkenyl optionally partially or fully halogenated, and
optionally substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl,
20 naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl,
thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned are optionally
substituted with 1 to 5 halogen, C₁₋₆ branched or unbranched alkyl optionally partially or
fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl,
bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, hydroxy, cyano, C₁₋₃ alkoxy
25 optionally partially or fully halogenated, NH₂C(O) or mono- or di(C₁₋₃)alkylaminocarbonyl; the C₃₋₁₀ branched or unbranched alkenyl is optionally interrupted
by one or more O, N or S(O)_m;
- cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl,
30 bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three C₁₋₃
alkyl groups;

cyano, halogen;

methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl;

silyl containing three C₁₋₄ independently branched or unbranched alkyl groups optionally

5 partially or fully halogenated;

C₂₋₆ branched or unbranched alkyl-C(O), C₂₋₆ branched or unbranched-S, C₂₋₆ branched or unbranched-S(O), C₂₋₆ branched or unbranched-S(O)₂;

C₂₋₆ alkynyl branched or unbranched carbon chain optionally partially or fully

10 halogenated, wherein one or more methylene groups are optionally replaced by O, NH and S(O)_m and wherein said alkynyl group is optionally independently substituted with 0-2 oxo groups, pyrroldinyl, pyrrolyl, one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or C₁₋₄ branched or unbranched
15 alkylamino optionally substituted by one or more halogen atoms;

each R₂, R₄, and R₅ is independently

a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, acetyl,

20 aroyl, C₁₋₄ branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;

C₁₋₆ alkoxy, hydroxy, amino, or mono- or di-(C₁₋₄ alkyl)amino, cyano, halogen;

25 OR₆;

nitro; or

mono- or di-(C₁₋₄ alkyl)amino-S(O)₂ optionally partially or fully halogenated, or H₂NSO₂;

30 each R₃ is independently:

hydrogen, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl,
pyrrolidinyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, thiazolyl,
oxazolyl, triazolyl, tetrazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl,
benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl,
5 benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl,
quinazolinyl, purinyl or indazolyl wherein each of the aforementioned is optionally
substituted with one to five phenyl, naphthyl, heterocycle or heteroaryl wherein the
heterocyclic and heteraryl moiety is as hereinabove described in this paragraph, C₁₋₆
branched or unbranched alkyl which is optionally partially or fully halogenated,
10 cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl,
bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halogen, hydroxy,
oxo, cyano, C₁₋₃ alkoxy optionally partially or fully halogenated, phenyloxy,
naphthyoxy, heteraryloxy wherein the heterocyclic moiety is as hereinabove described in
this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino,
15 heterocyclic or heteroaryl amino wherein the heterocyclic or heteroaryl moiety is as
hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkyl
aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-(C₁₋
3)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₇-C₁₋₅ alkyl, R₈-C₁₋₅
alkoxy, R₉-C(O)-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkyl(R₁₁)N, carboxy-mono- or di-(C₁₋₅)-alkyl-
20 amino;

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl,
tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocycle
selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine,
25 cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine,
cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline,
cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline,
cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole,
cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole,
30 cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and
cyclohexanothiophene; wherein the fused aryl or fused heterocyclic ring is optionally

independently substituted with 1 to 3 groups selected from phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thieryl, furyl, isoxazolyl, isothiazolyl, C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, halo, cyano, C₁₋₃ alkoxy optionally partially or fully halogenated,

- 5 phenyloxy, naphthoxy, heterocyclicoxy heteroaryloxy wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino, phenylamino, naphthylamino, heterocyclicamino or heteroarylarnino wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, NH₂C(O), a mono- or di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅
- 10 alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, an amino-C₁₋₅ alkyl, mono- or di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₁₂-C₁₋₅ alkyl, R₁₃-C₁₋₅ alkoxy, R₁₄-C(O)-C₁₋₅ alkyl and R₁₅-C₁₋₅ alkyl(R₁₆)N;

15 cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

20 cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl each optionally substituted with one to three C₁₋₃ alkyl groups;

25 C₁₋₄ branched or unbranched alkyl-phenyl-C(O)-C₀₋₄ branched or unbranched alkyl, C₁₋₄ branched or unbranched alkyl-C(O)-C₀₋₄ branched or unbranched alkyl, C₁₋₄ branched or unbranched alkyl-phenyl-S(O)_m-C₀₋₄ branched or unbranched alkyl;

30 C₁₋₆ branched or unbranched alkyl or C₁₋₆ branched or unbranched alkoxy each is optionally partially or fully halogenated or optionally substituted with R₁₇;

C₀₋₆ branched or unbranched alkyl optionally substituted with OR₁₈;
amino or C_{1-C5} branched or unbranched mono- or di-alkylamino optionally substituted
with R₁₉;

- 5 Cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy which
are optionally partially or fully halogenated and optionally substituted with one to three
C₁₋₃ alkyl groups optionally partially or fully halogenated, wherein one to three ring
methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;
- 10 R₂₀C(O)N(R₂₁)-, R₂₂O- or R₂₃R₂₄NC(O)-; R₂₆(CH₂)_mC(O)N(R₂₁)- or
R₂₆C(O)(CH₂)_mN(R₂₁)-;
- C₂₋₆alkenyl substituted by R₂₃R₂₄NC(O)-;
- 15 C₂₋₆ alkynyl branched or unbranched carbon chain optionally partially or fully
halogenated, wherein one or more methylene groups are optionally replaced by O, NH,
S(O), S(O)₂ or S and wherein said alkynyl group is optionally independently substituted
with 0-2 oxo groups, pyrroldinyl, pyrrolyl, one or more C₁₋₄ branched or unbranched
alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino,
- 20 piperidine, piperazine, imidazole, phenyl, pyridine, tetrazole, or C₁₋₄ branched or
unbranched alkylamino optionally substituted by one or more halogen atoms; or
aroyl;

25 R₆ is a:

C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated and optionally
substituted with R₂₆;

each R₇, R₈, R₉, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₇, R₁₉, R₂₅ and R₂₆ is independently:

nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl or alkylamino mono- or di-C₀₋₄ branched or unbranched optionally partially or fully halogenated;

5 each R₁₁ and R₁₆ is independently:

hydrogen or C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated;

R₁₈ is independently:

hydrogen or a C₁₋₄ branched or unbranched alkyl optionally independently substituted

10 with oxo or R₂₅;

R₂₀ is:

C₁₋₁₀ branched or unbranched alkyl optionally partially or fully halogenated, phenyl or pyridinyl;

15

R₂₁ is:

hydrogen or C₁₋₃ branched or unbranched alkyl optionally partially or fully halogenated;

each R₂₂, R₂₃ and R₂₄ is independently:

20 hydrogen, C₁₋₆ branched or unbranched alkyl optionally substituted by carbonylamino-mono- or di-C₁₋₃alkyl or amino-mono or diC₁₋₃alkyl or wherein said C₁₋₆ alkyl optionally partially or fully halogenated and optionally interrupted by one or more O, N or S, phenyl, pyridine, mono- or di-C₀₋₄ branched or unbranched alkyl optionally partially or fully halogenated and alkylamino;

25

or R₂₃ and R₂₄ taken together optionally form a heterocyclic or heteroaryl ring;

m = 0, 1 or 2;

30 X = O or S; and

the pharmaceutically acceptable derivatives thereof.

2. The compound according to claim 1 wherein

5

G is:

phenyl, naphthyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl,
benzocycloheptanyl, benzocycloheptenyl, indanyl, indenyl, benzofuran-3-one, 4H-
benzo[1,4]oxazine-3-one;

10

pyridinyl, pyridonyl, quinolinyl, dihydroquinolinyl, tetrahydroquinoyl, isoquinolinyl,
tetrahydroisoquinoyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzimidazolyl, benzthiazolyl,
benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl, dihydrobenzofuranyl,
dihydrobenzothiophenyl, benzoazolonyl, benzo[1,4]oxazin-3-onyl, benzodioxolyl,
15 benzo[1,3]dioxol-2-onyl, tetrahydrobenzopyranyl, indolyl, indolinyl, indolonyl,
indolinonyl, phthalimidyl;

oxetanyl, pyrrolidinyl, tetrahydrofuran-2-yl, tetrahydrothiophenyl, piperidinyl, piperazinyl,
morpholinyl, tetrahydropyranyl, dioxanyl, tetramethylene sulfonyl, tetramethylene
sulfoxidyl, oxazolinyl, thiazolinyl, imidazolinyl, tetrahydropyridinyl, homopiperidinyl,
20 pyrrolinyl, tetrahydropyrimidinyl, decahydroquinolinyl, decahydroisoquinolinyl,
thiomorpholinyl, thiazolidinyl, dihydrooxazinyl, dihydropyranyl, oxocanyl, heptacanyl,
thioxanyl or dithianyl;

wherein G is substituted by one or more R₁, R₂ or R₃.

25

3. The compound according to claim 2 wherein

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl,
benzimidazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl, benzpyrazolyl,
30 dihydrobenzofuranyl, dihydrobenzothiophenyl, indanyl, indenyl, indolyl, indolinyl,

indolonyl, indolinonyl, benzofuran-3-one or 4H-benzo[1,4]oxazine-3-one, wherein G is substituted by one or more R₁, R₂ or R₃;

Ar is:

5

naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indanyl, indenyl or indolyl each optionally substituted by one or more R₄ or R₅ groups;

10

L is a:

C₁₋₄ saturated or unsaturated branched or unbranched carbon chain;

wherein one or more methylene groups are optionally independently replaced by heteroatoms chosen from O, N and S(O)_m; and

15 wherein said L is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

Q is:

20 phenyl, naphthyl, pyridinyl or imidazolyl which are optionally substituted with one to three halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, hydroxy, amino, mono- or di-(C₁₋₃ alkyl)amino or mono- or di-(phenyl-C₁₋₃ alkyl)amino;

tetrahydropyranyl, tetrahydrofuranyl, morpholino, thiomorpholino, thiomorpholino
25 sulfoxide, piperidinyl, piperidinonyl, tetrahydropyrimidonyl, pentamethylene sulfide, pentamethylene sulfoxide or pentamethylene sulfone which are optionally substituted with one to three C₁₋₃ alkyl, C₁₋₃ alkoxy, hydroxy, mono- or di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, phenylamino-C₁₋₃ alkyl or C₁₋₃ alkoxy-C₁₋₃ alkyl;

30 each R₁ is independently:

C₁₋₅ branched or unbranched alkyl optionally partially or fully halogenated, and
optionally substituted with one to three C₃₋₆ cycloalkyl, hydroxy, phenyl, thienyl, furyl,
isoxazolyl or isothiazolyl; each of the aforesaid being optionally substituted with 1
to 5 halogen, C₁₋₃ alkyl which is optionally partially or fully halogenated, hydroxy, cyano
5 or C₁₋₃ alkoxy optionally partially or fully halogenated;

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl
optionally partially or fully halogenated and optionally be substituted with one to three
C₁₋₃ alkyl groups optionally partially or fully halogenated, cyano, hydroxyC₁₋₃alkyl or
10 phenyl; or an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl,
bicyclopentanyl or bicyclohexanyl wherein one to three ring methylene groups are
independently replaced by O, S, CHO, >C=O, >C=S or NH; or
15 silyl containing three C₁₋₄ independently branched or unbranched alkyl groups optionally
partially or fully halogenated;

each R₃ is independently:

hydrogen, phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrrolylidinyl, imidazolyl
20 or pyrazolyl, wherein each of the aforesaid is optionally substituted with one to
five phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this
paragraph, C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated,
cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl,
bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halogen, oxo,
25 hydroxy, cyano, C₁₋₃ alkoxy optionally be partially or fully halogenated, phenoxy,
naphthoxy, heteroaryloxy or heterocyclicoxy wherein the heteraryl or heterocyclic moiety
is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C₁₋₃)alkylamino,
phenylamino, naphthylamino, heterocyclic or heteroaryl amino wherein the heterocyclic
or heteroaryl moiety is as hereinabove described in this paragraph, NH₂C(O), a mono- or
30 di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, amino-C₁₋₅ alkyl, mono- or di-
(C₁₋₃)alkylamino-C₁₋₅ alkyl, amino-S(O)₂, di-(C₁₋₃)alkylamino-S(O)₂, R₇-C₁₋₅ alkyl, R₈-

C₁₋₅ alkoxy, R₉-C(O)-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkyl(R₁₁)N or carboxy-mono- or di-(C₁₋₅)-alkyl-amino;

5 C₁₋₃ alkyl or C₁₋₃ alkoxy optionally partially or fully halogenated or optionally substituted with R₁₇;

10 Cyclopropyloxy, cyclopentyloxy or cyclohexyloxy which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

15 C₀₋₆ branched or unbranched alkyl optionally substituted with OR₁₈; amino or C_{1-C₅} branched or unbranched mono- or di-alkylamino optionally substituted with R₁₉;

20 R₂₀C(O)N(R₂₁)-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆CH₂C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

25 C₂₋₄ alkenyl substituted by R₂₃R₂₄NC(O)-;

30 C₂₋₄ alkynyl branched or unbranched carbon chain optionally partially or fully halogenated and optionally independently substituted with 0-2 oxo groups, pyrroldinyl, pyrrolyl or one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

35 X is O;

and

40 R₂₃ and R₂₄ taken together optionally form imidazole, piperidine, morpholino, piperazine or a pyridinyl ring.

45

4. The compound according to claim 3 wherein:

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, pyrazinyl, benzothiophenyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indanyl, indolyl, 5 indolinyl, indolonyl, indolinonyl, cyclopropanyl, cyclohexanyl, piperidinyl or tetrahydropyran, wherein G is substituted by one or more R₁, R₂ or R₃;

Ar is naphthyl;

10 L is a:

C₁₋₄ alkyl or alkynyl branched or unbranched carbon chain;

wherein one methylene group is optionally independently replaced by heteroatoms chosen from O, S(O)_m and N; and

wherein said L is optionally substituted with 0-2 oxo groups and one or more C₁₋₂

15 alkyl optionally substituted by one or more halogen atoms;

Q is:

phenyl, pyridinyl, pyrimidinyl, imidazolyl, tetrahydropyranyl, morpholino,

20 thiomorpholino, thiomorpholino sulfoxide, piperidinyl, piperidinonyl or pentamethylene sulfoxide which are optionally substituted with one to three, amino, mono- or di-(phenyl-C₁₋₃ alkyl)amino, methyl, ethyl, methoxy, ethoxy, methoxymethyl or ethoxymethyl;

each R₁ is independently:

25 C₃₋₅ branched or unbranched alkyl, optionally partially or fully halogenated, and optionally substituted with phenyl substituted with 0 to 5 halogen, C₁₋₃ alkyl optionally partially or fully halogenated, hydroxy, cyano or C₁₋₃alkoxy optionally partially or fully halogenated;

30

cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, bicyclopentanyl or bicyclohexanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, CYANO, hydroxyC₁₋₃alkyl or phenyl; or an analog of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl,

- 5 bicyclopentanyl or bicyclohexanyl wherein one ring methylene group is replaced by O; and

silyl containing three C₁₋₂ independently branched or unbranched alkyl groups optionally partially or fully halogenated;

10

each R₃ is independently:

hydrogen, phenyl, pyridinyl, pyrimidinyl, pyrrolylidinyl, 2,5-pyrrolidin-dione, imidazolyl, pyrazolyl, each of the aforementioned is optionally substituted with one to 15 five C₁₋₃ alkyl optionally partially or fully halogenated, halogen, oxo, hydroxy, cyano or C₁₋₃ alkoxy optionally partially or fully halogenated;

C₁₋₃ alkyl or C₁₋₃ alkoxy optionally partially or fully halogenated or optionally substituted with R₁₇;

20

Cyclopropyloxy, cyclopentyloxy or cyclohexyloxy which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups optionally partially or fully halogenated, wherein one to three ring methylene groups are replaced independently by O, S(O)_m, CHOH, >C=O, >C=S or NH;

25

C₀₋₃ branched or unbranched alkyl optionally substituted with OR₁₈; amino or C_{1-C3} branched or unbranched mono- or di-alkylamino optionally substituted with R₁₉;

30 R₂₀C(O)N(R₂₁)-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆CH₂C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

C₂₋₄ alkenyl substituted by R₂₃R₂₄NC(O)-; or
C₂₋₄ alkynyl substituted with pyrroldinyl or pyrrolyl;
and
R₂₃ and R₂₄ taken together optionally form morpholino.

5

5. The compound according to claim 4 wherein:

10

G is phenyl, pyridinyl, pyridonyl, naphthyl, quinolinyl, isoquinolinyl, dihydrobenzofuranyl, indanyl, indolinyl, indolonyl, indolinonyl or cyclopropanyl, wherein G is substituted by one or more R₁, R₂ or R₃;

15

Ar is 1-naphthyl;

L is a: O-CH₂-, O-CH₂CH₂, O-CH₂CH₂CH₂, O-CH₂CH₂(CH₃), O-CH₂(CH₃)CH₂, NHCH₂, NHCH₂CH₂, NHCH₂CH₂CH₂, S(O)_mCH₂, S(O)_mCH₂CH₂, S(O)_mCH₂CH₂CH₂, CH₂CH₂, CH₂CH₂CH₂, O-CH₂C(O), HC≡C—CH₂ or HC≡C—CH₂O ;

20

each R₁ is independently:

C₃₋₅ branched or unbranched alkyl optionally partially or fully halogenated, and
25 optionally substituted with phenyl;
cyclopropyl, cyclopentanyl, cyclohexanyl or bicyclopentanyl optionally substituted with one to three methyl groups optionally partially or fully halogenated, CYANO, hydroxymethyl or phenyl;
30 cyclopentyloxy or cyclohexyloxy which are optionally partially or fully halogenated;

2-tetrahydrofuryl substituted by methyl; or trimethylsilyl;

each R₃ is independently:

hydrogen, phenyl, pyridinyl, pyrimidinyl, pyrrolylidinyl, 2,5-pyrrolidin-dione,
5 imidazolyl or pyrazolyl, wherein each of the aforementioned is optionally substituted
with C₁₋₂ alkyl optionally partially or fully halogenated;

C₁₋₃ alkyl or C₁₋₃ alkoxy each optionally be partially or fully halogenated or optionally
substituted with diethylamino;

10 C₀₋₃ branched or unbranched alkyl optionally substituted with OR₁₈;
amino or C_{1-C₃} branched or unbranched mono- or di-alkylamino optionally substituted
with R₁₉;

15 CH₃C(O)NH-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆CH₂C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

C₂₋₄ alkenyl substituted by R₂₃R₂₄NC(O)-; or

C₂₋₄ alkynyl substituted with pyrroldinyl or pyrrolyl;

20 R₂₃ and R₂₄ are H or R₂₃ and R₂₄ taken together optionally form morpholino; and
R₂₆ is morpholino.

25 6. The compound according to claim 5 wherein

G is phenyl substituted by one or more R₁, R₂ or R₃;

and

L is:

30 O, NH, CH₂ or S(O)_m.

7. The compound according to claim 4 wherein

G is phenyl or pyridinyl substituted by one or more R₁, R₂ or R₃;
Ar is 1-naphthyl;

5 L is:

C(O)CH₂- , >C(O), O, or CH₂;

each R₁ is independently:

10 C₃₋₅ branched or unbranched alkyl optionally partially or fully halogenated, and

each R₃ is independently:

hydrogen, C₁₋₃ alkyl or C₁₋₃ alkoxy each optionally be partially or fully halogenated or
15 optionally substituted with diethylamino;

CH₃C(O)NH-, R₂₂O- ; R₂₃R₂₄NC(O)-; R₂₆C(O)N(R₂₁)- or R₂₆C(O)CH₂N(R₂₁)-;

20 R₂₃ and R₂₄ are H or R₂₃ and R₂₄ taken together optionally form morpholino;
and
R₂₆ is alkylamino mono- or di-C₀₋₄ branched or unbranched.

25 8. The compound according to claim 7 wherein

G is pyridinyl

and

L is C(O)CH₂- , >C(O), O or CH₂.

30

9. A compound selected from:

1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-methoxy-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxyphenyl)-3-[4-(2-methyl-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2,3-dimethoxyphenyl)-3-[4-(2-methoxy-pyridin-4-yl-oxy)-naphthalen-1-yl]-urea;

5-tert-Butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}benzamide;

Morpholine-4-carboxylic acid (5-tert-butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}phenyl)amide;

N-(5-tert-Butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}phenyl)acetamide;

3-(5-tert-Butyl-2-methoxy-3-{3-[-(pyridin-4-yl-oxy)naphthalen-1-yl]ureido}phenyl)-1,1-diimethylurea;

1-[4-(2-Amino-pyridin-4-yloxy)-naphthalen-1-yl]-3-(5-tert-butyl-2,3-dimethoxy-phenyl)-urea;

1-(5-tert-Butyl-2,3-dimethoxy-phenyl)-3-[4-(2-methylamino-pyridin-4-yloxy)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2,3-dimethoxy-phenyl)-3-{4-[2-(1-phenyl-ethylamino)-pyridin-4-yloxy]-naphthalen-1-yl}-urea;

1-[4-(2-Amino-pyridin-4-yloxy)-naphthalen-1-yl]-3-(5-tert-butyl-2-methoxy-pyridin-3-yl)-urea;

1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-[4-(2-methylamino-pyridin-4-yloxy)-naphthalen-1-yl]-urea;

1-(5-tert-Butyl-2-methoxy-pyridin-3-yl)-3-{4-[2-(1-phenyl-ethylamino)-pyridin-4-yloxy]-naphthalen-1-yl}-urea;

1-(5-tert-Butyl-2-methylphenyl)-3-[4-(2-aminopyridin-4-yl-oxy)naphthalen-1-yl]urea;

1-(5-tert-Butyl-2-morpholin-4-yl-phenyl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea;

- 1-[3-Bromo-5-tert-butyl-2-(2-morpholin-4-yl-ethylamino)-phenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea;
- 5 1-[5-tert-butyl-2-methoxyphenyl]-3-[4-(2-(2-phenoxyethyl)morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea;
- 10 1-[5-tert-butyl-2-methylphenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea;
- 15 1-[5-tert-butyl-2-methylphenyl]-3-[4-(4-pyridinyloxy)-naphthalen-1-yl]-urea.
and the pharmaceutically acceptable salts thereof.
- 20 10. The compound according to claim 7 wherein the compound is selected from:
1-(5-tert-Butyl-2-methylphenyl)-3-[4-(2-aminopyridin-4-yl-oxy)naphthalen-1-yl]urea;
- 25 1-(5-tert-Butyl-2-morpholin-4-yl-phenyl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea,
1-[3-Bromo-5-tert-butyl-2-(2-morpholin-4-yl-ethylamino)-phenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea,
- 30 1-[5-tert-butyl-2-methoxyphenyl]-3-[4-(2-(2-phenoxyethyl)morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea,
1-[5-tert-butyl-2-methylphenyl]-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea,
1-[5-tert-butyl-2-methylphenyl]-3-[4-(4-pyridinyloxy)-naphthalen-1-yl]-urea;
1-[5-tert-butyl-2-methylphenyl]-3-[4-(3-pyridinyloxy)-naphthalen-1-yl]-urea
35 and the pharmaceutically acceptable salts thereof.

11. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claims 1 or 9.

5

12. A method of treating a disease mediated by cytokines which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound according to claim 1 or 9.

10

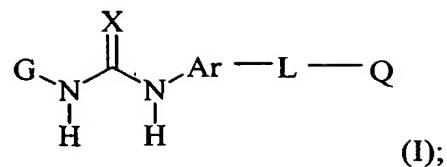
13. The method according to claim 12 wherein the cytokine-mediated disease is selected from rheumatoid arthritis, osteoarthritis, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, graft versus host disease, systemic lupus erythematosus, diabetes, toxic shock syndrome, osteoporosis, Alzheimer's disease, acute and chronic pain, contact dermatitis and atherosclerosis.

15

14. A method of treating a neutrophil-mediated disease selected from stroke, myocardial infarction, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis, hemodialysis, leukopheresis, granulocyte transfusion associated syndromes and necrotizing enterocolitis, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound according to claim 1 or 9.

20
25

15. A method of making a compound of the formula(I):



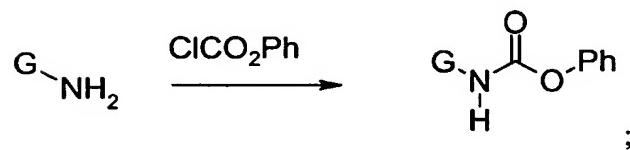
wherein X is O and G, Ar, L and Q are as defined in claim 1,

said method comprising:

5

- a) reacting an arylamine with phenyl chloroformate in a suitable solvent with a suitable base at 0 – 85°C for 2 – 24 hours:

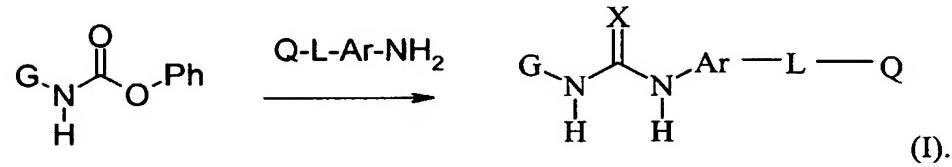
10



15

- b) reacting the product of step a) with an arylamine shown below in a non-protic anhydrous at 0 – 110°C for 2 – 24 hours, to produce a compound of the formula (I):

20



| | |
|-----------------|----------------|
| Intern: | Application No |
| PCT/US 00/31582 | |

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D295/08 A61P29/00 C07D213/73 C07D295/12 C07D213/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| P, X | WO 00 55139 A (BOEHRINGER INGELHEIM PHARMA) 21 September 2000 (2000-09-21) claim 1; examples 18,19,38 --- | 1-15 |
| P, X | WO 00 55152 A (BOEHRINGER INGELHEIM PHARMA) 21 September 2000 (2000-09-21) claim 1 --- | 1-15 |
| X | WO 99 23091 A (BOEHRINGER INGELHEIM PHARMA) 14 May 1999 (1999-05-14) cited in the application claim 1 --- | 1-15 |
| X | US 5 162 360 A (CRESWELL MARK W ET AL) 10 November 1992 (1992-11-10) cited in the application claim 1 --- | 1-5 -/- |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

28 February 2001

Date of mailing of the international search report

29.03.01

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Gettins, M

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/31582

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 98 52558 A (CHEN JINSHAN ;PAULSEN HOLGER (DE); RANGES GERALD (US); RENICK JOEL) 26 November 1998 (1998-11-26) cited in the application claim 1 --- | 1-15 |
| X | WO 96 25157 A (HERTZBERG ROBERT PHILIP ;JUREWICZ ANTHONY JOSEPH (US); RUTLEDGE ME) 22 August 1996 (1996-08-22) claim 1 --- | 1-15 |
| X | WO 99 32111 A (BAYER AG) 1 July 1999 (1999-07-01) claim 1 --- | 1-15 |
| X | WO 99 32110 A (BAYER AG) 1 July 1999 (1999-07-01) claim 1 --- | 1-15 |
| X | WO 99 32106 A (BAYER AG) 1 July 1999 (1999-07-01) claim 1 --- | 1-5 |
| X | WO 99 32463 A (KLIJANOWICZ JAMES E ET AL) 27 December 1983 (1983-12-27) claim 1 ----- | 1-15 |
| X | US 4 423 126 A (KLIJANOWICZ JAMES E ET AL) 27 December 1983 (1983-12-27) claim 1 ----- | 1-10 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/31582

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 00 31582

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) where Ar is 1-naphthyl and G is phenyl or pyridyl. This covers all of the compounds which are specifically claimed and/or have been tested. . Claims 6-10 can be considered to have been fully searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

| | |
|-----------------|----------------|
| Intern | Application No |
| PCT/US 00/31582 | |

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|--|---|------------------|-------------------------|------------|------------------|
| WO 0055139 | A | 21-09-2000 | AU | 2881700 A | 04-10-2000 |
| WO 0055152 | A | 21-09-2000 | NONE | | |
| WO 9923091 | A | 14-05-1999 | AU | 1367599 A | 24-05-1999 |
| | | | EP | 1028953 A | 23-08-2000 |
| US 5162360 | A | 10-11-1992 | NONE | | |
| WO 9852558 | A | 26-11-1998 | AU | 7585498 A | 11-12-1998 |
| | | | DE | 1019040 T | 08-02-2001 |
| | | | EP | 1019040 A | 19-07-2000 |
| | | | ES | 2151467 T | 01-01-2001 |
| WO 9625157 | A | 22-08-1996 | EP | 0809492 A | 03-12-1997 |
| | | | JP | 11503110 T | 23-03-1999 |
| | | | NO | 983737 A | 14-10-1998 |
| | | | US | 5886044 A | 23-03-1999 |
| | | | US | 5780483 A | 14-07-1998 |
| WO 9932111 | A | 01-07-1999 | AU | 1997199 A | 12-07-1999 |
| | | | EP | 1041982 A | 11-10-2000 |
| WO 9932110 | A | 01-07-1999 | AU | 1997099 A | 12-07-1999 |
| | | | EP | 1043995 A | 18-10-2000 |
| WO 9932106 | A | 01-07-1999 | AU | 2198999 A | 12-07-1999 |
| | | | EP | 1047418 A | 02-11-2000 |
| | | | NO | 20003232 A | 21-08-2000 |
| WO 9932463 | A | 01-07-1999 | AU | 1939999 A | 12-07-1999 |
| | | | EP | 1042305 A | 11-10-2000 |
| US 4423126 | A | 27-12-1983 | CA | 1206972 A | 01-07-1986 |
| | | | DE | 3365436 D | 25-09-1986 |
| | | | EP | 0095899 A | 07-12-1983 |
| | | | JP | 58215460 A | 14-12-1983 |
| | | | US | 4536598 A | 20-08-1985 |